EXHIBIT 9

Yearly Rupture or Dissection Rates for Thoracic Aortic Aneurysms: Simple Prediction Based on Size

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Background. **Prior work has clarified the cumulative, lifetime risk of rupture or dissection based on the size of thoracic aneurysms. Ability to estimate simply the yearly rate of rupture or dissection would greatly enhance clinical decision making for specific patients. Calculation of such a rate requires robust data.**

Methods. **Data on 721 patients (446 male, 275 female; median age, 65.8 years; range, 8 to 95 years) with thoracic aortic disease was prospectively entered into a computerized database over 9 years. Three thousand one hundred fifteen imaging studies were available on these patients. Five hundred seventy met inclusion criteria in terms of length of follow-up and form the basis for the survival analysis. Three hundred four patients were dissection-free at presentation; their natural history was followed for rupture, dissection, and death. Patients were excluded from analysis once operation occurred.**

Results. **Five-year survival in patients not operated on was 54% at 5 years. Ninety-two hard end points were realized in serial follow-up, including 55 deaths, 13 ruptures, and 24 dissections. Aortic size was a very strong predictor of rupture, dissection, and mortality. For aneurysms greater than 6 cm in diameter, rupture occurred at 3.7% per year, rupture or dissection at 6.9% per year, death at 11.8%, and death, rupture, or dissection at 15.6% per year. At size greater than 6.0 cm, the odds ratio for rupture was increased 27-fold ($p = 0.0023$). The aorta grew at a mean of 0.10 cm per year. Elective, preemptive surgical repair restored life expectancy to normal.**

Conclusions. **This study indicates that (1) thoracic aneurysm is a lethal disease; (2) aneurysm size has a profound impact on rupture, dissection, and death; (3) for counseling purposes, the patient with an aneurysm exceeding 6 cm can expect a yearly rate of rupture or dissection of at least 6.9% and a death rate of 11.8%; and (4) elective surgical repair restores survival to near normal. This analysis strongly supports careful radiologic follow-up and elective, preemptive surgical intervention for the otherwise lethal condition of large thoracic aortic aneurysm.**

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Historically, the timing of operation for patients with thoracic aortic aneurysms (TAA) was established clinically, with scant reference to hard scientific and statistical data. Given the risks associated with surgical procedures involving the thoracic aorta, such data are essential for optimal treatment of patients with TAA.

Treatment decisions should involve a balancing of the risk of complications caused by the dilated aorta with the risk of complications from the operation itself. The most devastating complications of TAA are dissection, which may lead to arterial occlusion and end-organ ischemia, and rupture, which is almost invariably fatal [1, 2]. Rupture rates in patients not treated surgically are high, ranging from 21% to 74% [1, 3, 4]. However, the risk of operation is also pertinent: elective operation carries a mortality rate of approximately 5% to 9% [4–6]. For emergency operation the mortality rate may be as high as 57% [4, 6]. In addition, the risk of spinal cord injury, particularly in operations on the descending aorta, is significant [7]. Also, stroke occurs with disturbing frequency in operations on both the ascending and descending aortas [8].

A recent MEDLINE search identified nearly 1,000 articles addressing the surgical treatment of TAAs, but less than 10 specifically examining the natural risk of rupture or dissection in aneurysms not treated surgically. In deciding whether or not to operate on the basis of the clinical characteristics of patients there is little hard scientific guidance.

Our group has previously demonstrated that the risk of dissection or rupture increases with aneurysm size [6]. We reported a cumulative, lifetime risk of rupture or dissection by the time specific aortic sizes were reached. Data were not robust enough to permit estimation of yearly risk of rupture or dissection based on size. Juvonen and associates [9] subsequently developed an elegant model using an exponential equation, based on a variety of risk factors, to enable the calculation of rupture risk in specific patients.

The database of the Yale Center for Thoracic Aortic Disease has now grown large enough to permit analyses yielding a simple prediction of yearly rates of rupture or

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Table 1. Demographic Data on 304 Patients With Thoracic Aortic Aneurysms[a]

Variable	n	%	Mean	Median	Range
Sex (male)	179	58.9			
Age at presentation (y)			59.8	65.8	8.8 to 93.7
Initial aortic size (cm)			5.0	4.7	3.5 to 11.0
Radiologic follow-up (mo)			43.1	31.6	0.0 to 262.6
Marfan syndrome	28	9.2			
Aneurysm size					
3.5 to 3.9 cm	33	10.9			
4.0 to 4.9 cm	133	43.8			
5.0 to 5.9 cm	78	25.7			
≥ 6.0 cm	60	19.7			
Aneurysm location					
Ascending	219	72.0			
Arch	18	5.9			
Descending	28	9.21			
Thoracoabdominal	39	12.8			
Hypertension (n = 240)	142	59.1			
Cardiac disease (n = 219)	96	43.8			
Tobacco use (n = 220)	81	36.8			
Pulmonary disease (n = 225)	47	20.9			
Carotid disease (n = 209)	23	11.0			
Renal disease (n = 220)	30	13.6			
Coronary artery disease (n = 304)	82	27.0			
Congestive heart failure (n = 304)	34	11.2			
Stroke or transient ischemic attacks (n = 304)	25	8.2			
Abdominal aortic aneurysm (n = 304)	31	10.2			

[a] Totals may not add up to 100% because of rounding.

dissection based on aneurysm size for patients with TAA. It is hoped that these data will be of value in decision making for patients being evaluated for surgical extirpation of asymptomatic aortic aneurysms.

Material and Methods

Patient Population

Our database now includes information on 721 patients with TAAs. There are 2,276 total patient-years of follow-up and 1,383 patient-years of follow-up preceding operation, from which natural history can be assessed. We have analyzed 3,115 radiographic studies (985 computed tomographic scans, 418 magnetic resonance imaging scans, 139 transesophageal echocardiography studies, 1,344 transthoracic echocardiography studies, and 229 angiographic studies) of patients with thoracic aortic disease. Among these patients, 570 met inclusion criteria in terms of longitudinal length of follow-up and form the basis of the survival estimates in this series. Of those, 304 were free of preexisting dissection and form the basis of the current analyses of rates of rupture or dissection.

Hospital chart review was then conducted on each identified patient, and the data were entered into a computerized database. Data recovered from hospital records and computer files were cross-referenced with hospital discharge abstract data monitored by the Connecticut Hospital Association and the Connecticut State Mortality Records. The database is maintained as part of the ongoing studies at the Yale Center for Thoracic Aortic Disease, a major referral center for southern New England. Patients were recruited and followed between 1985 and 2000.

Inclusion criteria for the subgroup of 304 patients were as follows: aortic size at least 3.5 cm and age older than 6 years at presentation, absence of congenital aortic malformations (for example, aortic coarctation), and at least one size measurement before referral for operative repair. Patients with preexisting dissection were also excluded from analysis because dissection was an end point to this portion of the study. These 304 patients form the basis for the analysis of complication rates. Patient characteristics are shown in Table 1. There were 179 men and 125 women. Median age in this population was 65.8 years and ranged from 8.8 to 93.7 years. Available radiologic follow-up in these patients ranged from 0 to 262 months with a median of 31.6 months. There were 28 patients with Marfan syndrome and no patients identified with other inherited systemic connective tissue diseases.

Among the 92 hard end points realized in serial follow-up of these patients were 55 deaths, 13 documented ruptures, and 24 documented new, acute aortic dissections (Table 2). We examined the mortality records of all patients. Ten mortalities could be attributed definitively (on the basis of death certificates and autopsy reports) to causes other than aortic aneurysm. It is likely that some

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Table 2. Distribution of 92 End Points[a]

Events	No. Patients
Dissection, rupture and death	2
Dissection, rupture (no death)	2
Dissection, death (no rupture)	5
Rupture and death (no dissection)	4
Rupture alone	5
Dissection alone	15
Death alone	44

[a] Some patients satisfied multiple end points, leading to the total of the 92 specific events.

of the remaining mortality represented aneurysm rupture and that the true incidence of rupture in this population was even higher than in our tabulation.

Statiscal Methods

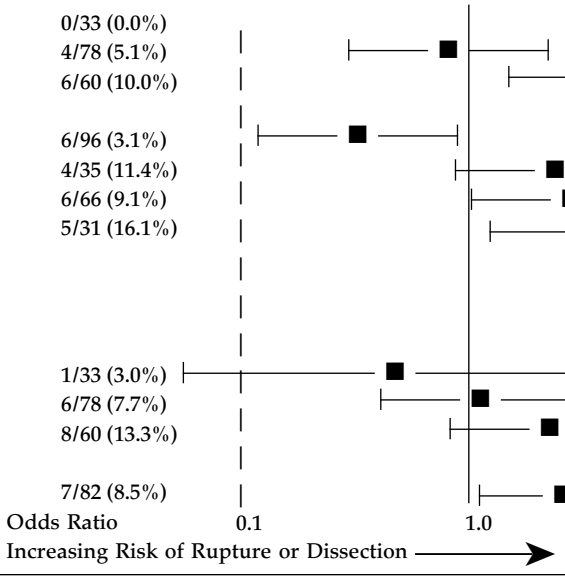
Statistical methods were used to identify and estimate risk factors for the following outcomes: annual growth rates of aneurysms, cumulative incidence of major complications, survival free from major complications, and overall long-term survival. When analyzing smoking history, hypertension, and the presence of cardiac, pulmonary, or renal disease, patients were stratified according to established criteria of risk for complications from vascular disease [10], and the analysis was performed both with the stratified severity levels and with a dichotomous variable indicating the presence of disease of any severity. Results are not shown for the analysis with stratified levels because they did not provide any additional information.

The methods of statistical analysis included χ^2 test for comparisons of dichotomous risk factors (history of coronary artery disease, congestive heart failure, abdominal aortic aneurysm, and so forth) with negative outcomes (rupture, dissection, death); Mantel-Haenszel χ^2 test for comparisons taking into consideration disease severity (cardiac disease, pulmonary disease, progressively larger aneurysms, and so forth); and the Wilcoxon test for comparisons of continuous variables with negative outcomes ($p < 0.05$). Logistic regression analysis of the cumulative incidence was used to evaluate the influence of risk factors for rupture or dissection. Life-table estimates (Kaplan-Meier) were calculated using the LIFETEST procedure of SAS 6.12 for PowerPC (SAS Institute, Cary, NC) with the log-rank test for difference between strata. Average yearly rates were calculated from this life-table analysis using $-\ln(X)/5$ where X is the complication-free survival after 5 years. The Cox regression model (using the PHREG procedure) was used to identify the most predictive variables.

Variables were entered into the models in a forward stepwise manner in the following order: initial aortic size, aneurysm location, age at presentation, and sex, followed by variables indicating a history of hypertension, abdominal aortic aneurysm, tobacco use, coronary artery disease, pulmonary disease, stroke, peripheral vascular dis-

Table 3. Univariate Analysis of Risk Factors Predictive of Rupture or Dissection

Risk Factor	Complication Rate	Odds Ratio (with 95% CI)	*p* Value
Risk factors for rupture			
Initial aortic size			
3.5 to 3.9 cm	0/33 (0.0%)		0.198
5.0 to 5.9 cm	4/78 (5.1%)	1.303	0.666
6.0 cm	6/60 (10.0%)	3.762[a]	0.014[a]
Sex (male)	6/96 (3.1%)	0.365[a]	0.044[a]
Marfan syndrome	4/35 (11.4%)	2.839	0.071
Aneurysm location (desc/TA)	6/66 (9.1%)	3.243[a]	0.032[a]
AAA	5/31 (16.1%)	4.663[a]	0.003[a]
Risk factors for dissection			
Initial aortic size			
3.5 to 3.9 cm	1/33 (3.0%)	0.337	0.272
5.0 to 5.9 cm	6/78 (7.7%)	0.963	0.939
6.0 cm	8/60 (13.3%)	2.192	0.081
CAD	7/82 (8.5%)	2.370[a]	0.028[a]

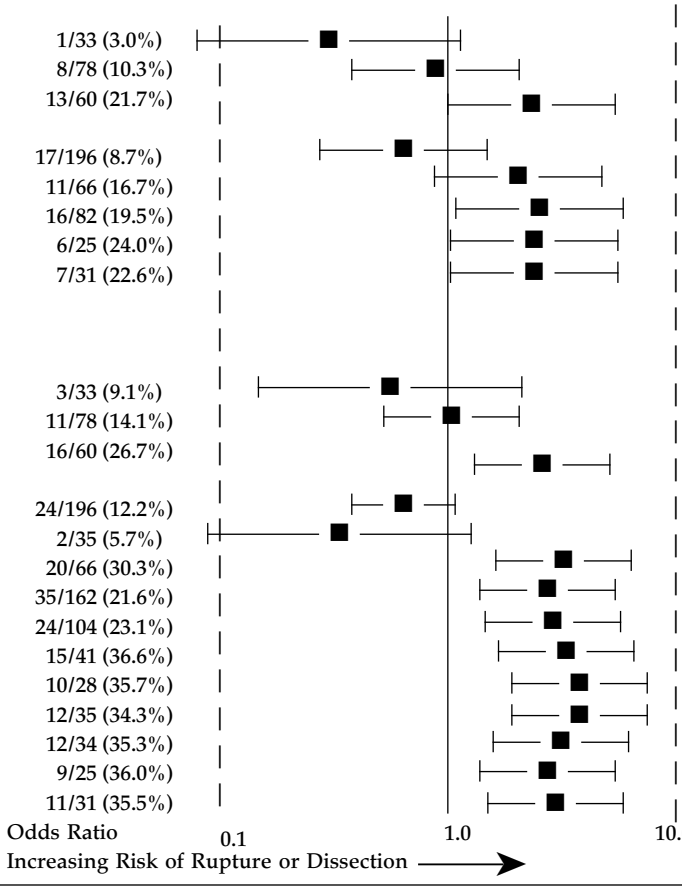


[a] Statistically significant result. All of the following variables were analyzed: initial aortic size, sex, Marfan syndrome, aneurysm location, hypertension, cardiac disease, tobacco history, pulmonary disease, carotid disease, renal disease, coronary artery disease (CAD), congestive heart failure, prior cerebrovascular accident, and history of abdominal aortic aneurysm (AAA). Only results for initial aortic size and those where $p < 0.10$ are shown. Bars on graph indicate 95% confidence intervals (CI), odds ratios cannot be calculated when the incidence of disease is zero.

desc/TA = descending or thoracoabdominal aorta.

Table 4. Univariate Analysis of Risk Factors Predictive of Rupture or Dissection or of Mortality

Risk Factor	Complication Rate	Odds Ratio (with 95% CI)		*p* Value
Risk factors for rupture or dissection				
Initial aortic size				
3.5 to 3.9 cm	1/33 (3.0%)		0.233	0.126
5.0 to 5.9 cm	8/78 (10.3%)		0.919	0.844
6.0 cm	13/60 (21.7%)		3.098	0.003[a]
Sex (male)	17/196 (8.7%)		0.475	0.027[a]
Aneurysm location (desc/TA)	11/66 (16.7%)		1.927	0.096
CAD	16/82 (19.5%)		2.303	0.016[a]
Prior CVA	6/25 (24.0%)		2.554	0.054
AAA	7/31 (22.6%)		2.386	0.056
Risk factors for mortality				
Initial aortic size				
3.5 to 3.9 cm	3/33 (9.1%)		0.421	0.155
5.0 to 5.9 cm	11/78 (14.1%)		0.679	0.288
6.0 cm	16/60 (26.7%)		1.911	0.054
Sex (male)	24/196 (12.2%)		0.367	0.001[a]
Marfan syndrome	2/35 (5.7%)		0.241	0.039[a]
Aneurysm location (desc/TA)	20/66 (30.3%)		2.472	0.004[a]
Hypertension	35/162 (21.6%)		2.035	0.041[a]
Cardiac disease	24/104 (23.1%)		2.206	0.021[a]
Pulmonary disease	15/41 (36.6%)		2.486	0.011[a]
Carotid disease	10/28 (35.7%)		3.278	0.005[a]
Renal disease	12/35 (34.3%)		3.165	0.003[a]
CHF	12/34 (35.3%)		2.727	0.008[a]
Prior CVA	9/25 (36.0%)		2.717	0.020[a]
AAA	11/31 (35.5%)		2.718	0.011[a]



[a] Statistically significant result. All of the following variables were analyzed: initial aortic size, sex, Marfan syndrome, aneurysm location, hypertension, cardiac disease, tobacco history, pulmonary disease, carotid disease, renal disease, coronary artery disease (CAD) congestive heart failure (CHE), prior cerebrovascular accident (CVA), and history of abdominal aortic aneurysm (AAA). Only results for initial aortic size and those where $p < 0.10$ are shown. Bars on graph indicate 95% confidence intervals (CI), odds ratios cannot be calculated when the incidence of disease is zero. desc/TA = descending or thoracoabdominal aorta.

ease, congestive heart failure and renal disease, and Marfan disease. Threshold for entry into the model for both logistic regression and Cox regression was p less than 0.10.

ANEURYSM GROWTH RATES. Of the 304 patients included in the complication analysis, serial imaging (two or more studies) before operative repair was available in 203. An additional 129 patients presenting initially with chronic dissection were able to be included in growth rate analysis. The period of serial radiologic follow-up before operation ranged from 0 to 171.7 months, with a median of 19.1 months. This sample of 332 patients was followed longitudinally and was used to estimate growth rates, and to identify risk factors for higher growth rates. Once patients underwent surgical repair, subsequent measurements were excluded from analysis. Growth rate estimates were obtained by means of a multivariable regression analysis in which aneurysm growth followed an exponential path. In particular, the natural logarithm of the difference between the last measured size and the first measured size was related to the time interval between the two tests and interactions between this time variable and risk factors. This statistical method was previously described in detail by our team [11].

Risk factors analyzed included chronic dissection, initial aneurysm size (stratified into the following groups: less than 4.0 cm, 4 to 4.9 cm, 5 to 5.9 cm, and 6 cm or greater), and aneurysm location (ascending aorta or aortic arch versus descending aorta or thoracoabdominal aorta, and each location separately). Selected additional risk factors were analyzed for their impact on growth, as indicated below.

COMPLICATION RATES. The incidence of acute dissection or rupture (or both) was evaluated by both descriptive and multivariable analyses. Rupture and dissection were confirmed by at least one of the following: autopsy, operation, death certificate, or computed tomography or magnetic resonance imaging. Patients who underwent

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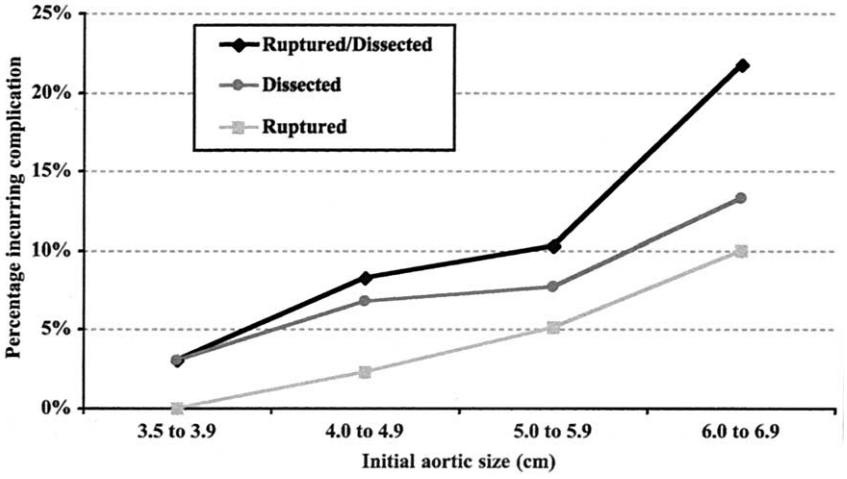

Fig 1. Cumulative incidence of acute dissection or rupture as a function of initial aneurysm size. The increase in rupture or dissection with increasing size is statistically significant (p = 0.003), as is the increase in the incidence of rupture (p = 0.006).

surgical treatment were excluded from subsequent analysis.

The multivariable analysis specifies a logistic regression model relating occurrence of rupture or acute dissection to each of the following: initial aortic size (both stratified and unstratified), aneurysm location, age at presentation, sex, Marfan syndrome, cardiac status, hypertension status, pulmonary disease, renal disease, history of smoking, and a history of abdominal aortic aneurysm, coronary artery disease, congestive heart failure, or stroke.

COMPLICATION-FREE SURVIVAL AND LONG-TERM SURVIVAL ANALYSIS. Five-year survival estimates were calculated by life-table estimates (Kaplan-Meier). For these analyses, patients were entered into the analysis at the time of initial presentation. For the complication-free survival analysis, patients were censored when they were lost to follow-up, underwent surgical correction, or died without rupture or dissection. Only two major complications, rupture, dissection, or both, were considered in analyzing complication-free survival. For the long-term survival analysis, patients were censored when they were lost to follow-up or underwent surgical correction. Yearly complication rates for subgroups were estimated from the life-table analysis and represent the mean complication rate for each year during the first 5 years after diagnosis.

The specific factors tested for survival differences included initial aortic size (both stratified and unstratified), aneurysm location, age at presentation, sex, Marfan syndrome, cardiac status, hypertension status, pulmonary disease, renal disease, history of smoking, and history of abdominal aortic aneurysm, coronary artery disease, congestive heart failure, or stroke.

Results

Aneurysm Characteristics

The distribution of aneurysms by initial size is shown in Table 1. Aneurysms of the ascending aorta were substantially more common than the others. The mean initial aortic size for patients with Marfan syndrome was significantly smaller than for those without (4.6 versus 5.1 cm, $p = 0.0001$); in addition, aneurysms of the aortic arch and thoracoabdominal aorta were significantly larger than those of the ascending aorta (5.9 and 5.7 versus 4.8 cm, $p < 0.005$).

Aneurysm Growth Rates

Aneurysm growth rates were calculated as described earlier. Aneurysms in the descending or thoracoabdominal region had substantially higher growth rates (0.19 cm/y) than those in the ascending aorta or aortic arch (0.07 cm/y). A similar difference in growth rates was

Table 5. Logistic Regression Analysis of Factors Predicting Rupture or Acute Dissection (Dependent Variables)[a]

Regression Analysis Variable	Variable Estimate	Standard Error	*p* Value	Odds Ratio[c]	
Intercept term	−2.4296	0.4376	0.0001		
Aortic size					
5.0–5.9 cm	0.9120	0.5448	0.0941	2.498	(0.856–7.241)
≥ 6.0 cm[d]	1.6538[d]	0.5285	0.0018[d]	5.227[d]	(1.855–14.727)
Sex (male)	−1.0792[d]	0.4490	0.0162[d]	0.340[d]	(0.141–0.819)
Cerebrovascular accident	1.0683	0.5747	0.0630	2.911	(0.944–8.978)
Marfan disease	1.2995[d]	0.6165	0.0350[d]	3.668[d]	(1.096–12.278)

[a] This variable equals 1 if the patient incurred a rupture or acute dissection and 0 otherwise. [b] Criteria for assessing model fit: −2 Log L, intercept only, 166.057; intercept and covariates, 145.359; χ^2 for covariates, 20.698 with five degrees of freedom ($p = 0.0009$). [c] 95% confidence intervals on odds ratios are given in parentheses. [d] Statistically significant at 5% level.

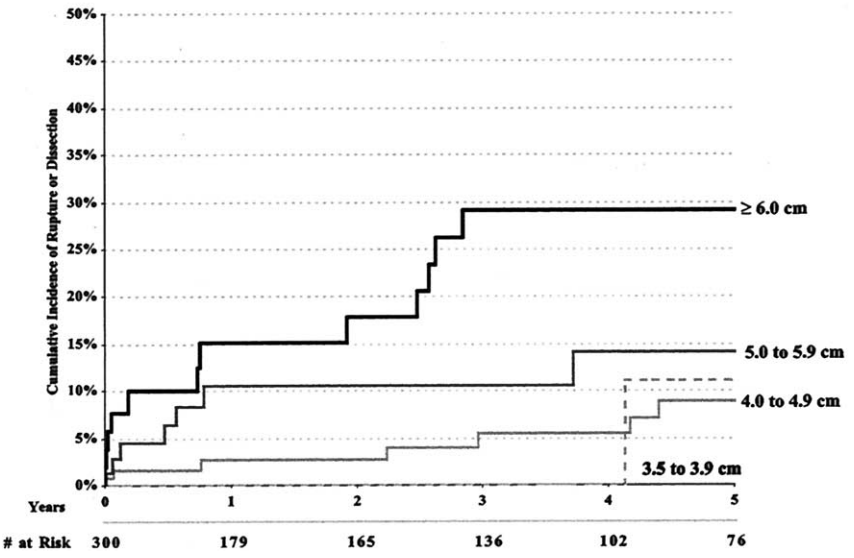

Fig 2. Kaplan-Meier cumulative hazard function of rupture or dissection. Five-year hazard estimates are illustrated for patients as a function of initial aneurysm size (p = 0.006).

found with dissected (0.14 cm/y) versus nondissected (0.09 cm/y) aortas. Patients with Marfan syndrome and those with a history of pulmonary disease also had higher growth rates. Although these were strong trends, the sample sizes were not large enough to demonstrate statistical significance.

Complication Rates

DESCRIPTIVE STATISTICS. Univariate analysis of risk factors predictive of rupture is shown in the top of Table 3. Initial aortic size of 6.0 cm or greater was associated with nearly a fourfold increase in the incidence of rupture. Other significant univariate predictors of rupture included location of the aneurysm in the descending or thoracoabdominal aorta and a history of abdominal aortic aneurysm. In addition, male sex conferred significant protection from rupture. The analysis in the bottom of Table 3 shows risk factors for dissection. Size showed a strong predictive trend in this analysis. A history of coronary artery disease was associated with a higher incidence of dissection.

The incidence of rupture or dissection, analyzed together, is shown at the top of Table 4. Size was a powerful predictor of these complications. The protective effect of male sex was consistent, as was the increased risk associated with the presence of other vascular diseases including coronary artery disease, abdominal aortic aneurysm, or a history of stroke. The bottom of Table 4 indicates that nearly all comorbidities, but particularly vascular diseases, were associated with an increased incidence of death before surgical correction in this population. Aortic size was again a powerful predictor of mortality before operation. The impact of aortic size on rupture and dissection is illustrated in Figure 1.

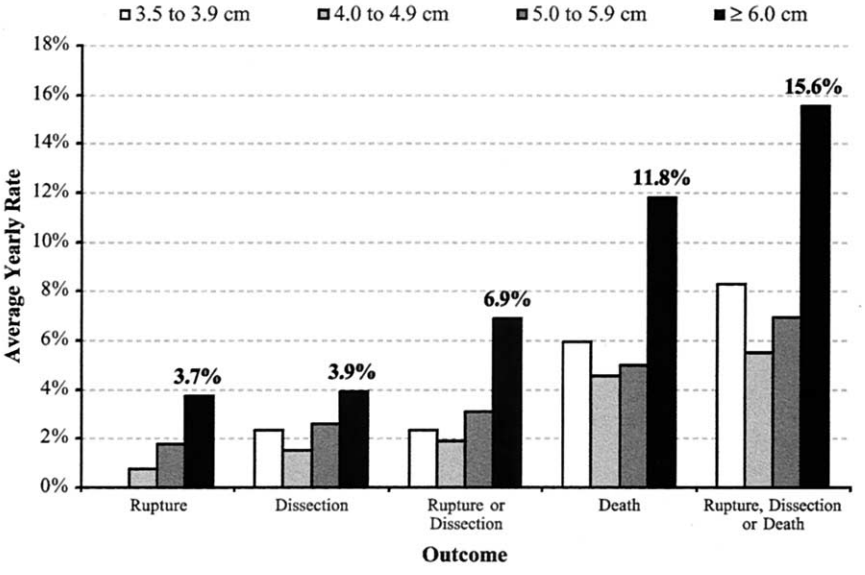

Fig 3. Average yearly rates of negative outcomes (rupture, dissection, and death). These estimates represent the average rate during the first 5 years after presentation.

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Table 6. Proportional Hazards Regression of Factors Predicting Increased Rates of Rupture or Dissection

Regression Analysis Variable	Variable Estimate	Standard Error	*p* Value	Odds Ratio[c]	
Size ≥ 6.0 cm[d]	1.101374[d]	0.38774	0.0045[d]	3.008	(1.407–6.432)
CVA[e]	1.041497[b]	0.46201	0.0242[c]	2.833[e]	(1.146–7.008)

[a] This variable equals 1 if the patient incurred a rupture and 0 otherwise. [b] Criteria for assessing model fit, −2 Log L; without covariates, 264.883; with covariates, 253.401; χ^2 for covariates, 11.482 with two degrees of freedom ($p = 0.0032$). [c] 95% confidence intervals on odds ratios are given in parentheses. [d] Statistically significant at the 0.5% level. [e] Statistically significant at the 5% level.

The results of a multivariable regression analysis examining risk factors predictive of rupture or dissection are given in Table 5. Increasing aortic size was a strong predictor of increasing risk of rupture or acute dissection. Size of 6.0 cm or greater was associated with a fivefold increase in cumulative risk of complications (odds ratio, 5.227; 95% confidence interval, 1.885 to 14.727). Male sex was associated with a relative protective effect, whereas Marfan disease was associated with a relative risk of 3.7 ($p < 0.035$). In addition, a history of stroke was associated with increasing complication rates.

INCIDENCE OF RUPTURE, DISSECTION, AND DEATH AS A FUNCTION OF TIME. The incidence of rupture or dissection with time as a function of initial aneurysm size is given in Figure 1. The rate of ruptures and dissections was significantly higher in patients with higher initial aortic size ($p = 0.006$; Fig 2). At aortic sizes of 6.0 cm or greater, there is a marked step up in the average yearly rate of complications (rupture or acute dissection) to 6.9% per year (Fig 3). Proportional hazards regression demonstrates that the hazard function for rupture or dissection is more than three times worse for patients with a size of 6.0 cm or greater than for those with a size between 4.0 and 4.9 cm. Again, vascular comorbidity in the form of a history of stroke was associated with increasing risk (odds ratio, 2.833; 95% confidence interval, 1.146 to 7.008; Table 6).

The importance of size is vividly apparent when rupture is analyzed alone (Figs 3, 4). The risk of rupture with time is 11 times worse with aortic size of 5.0 to 5.9 cm and nearly 27 times worse with size of 6.0 cm or greater when each is compared with aneurysms of size less than 4.0 cm (Table 7). Similar risk with increased aortic size is seen when dissection is analyzed alone (Figs 3, 5).

As described above, nearly all risk factors were predictive of increased risk of death before operation in a univariate analysis (Table 4). However, when analyzing the survival of these patients before operative repair with proportional hazards analysis, only a history of pulmonary disease (risk ratio, 2.257; 95% confidence interval, 1.071 to 4.755) and increasing age at presentation (risk ratio, 1.095 per year; 95% confidence interval, 1.050 to 1.141) were predictive of poor survival.

The yearly rates of complications demonstrate a dramatic increase at sizes greater than 6 cm (Fig 3). This step up in the risk of negative outcomes is clearly evident when rupture, dissection, and death before surgical repair are considered as end points together (Fig 3), with a mean yearly rate more than four times as high in patients with a size of 6 cm or greater than in those with smaller aneurysms.

Long-Term Survival

Overall long-term survival as a function of initial aortic size is shown in Figure 6. This figure shows the natural history survival before operation. Five-year survival of patients with aneurysms greater than 6 cm was only 56%.

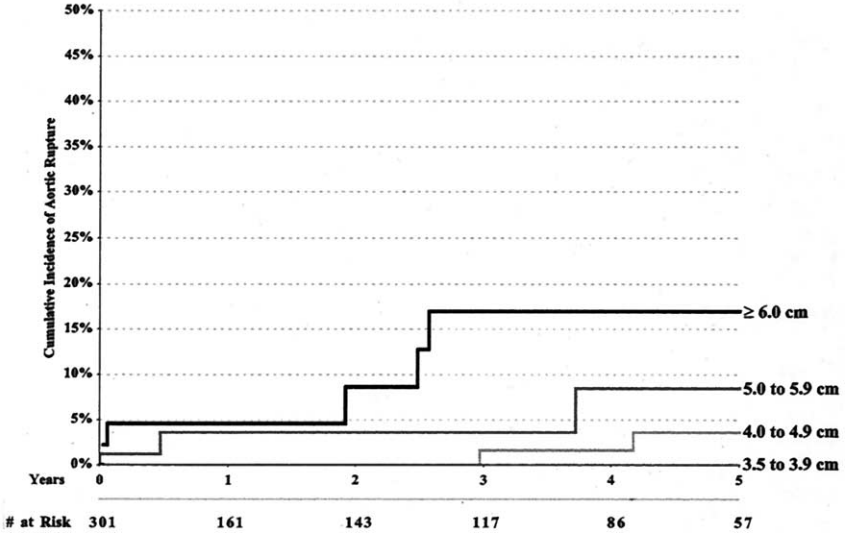

Fig 4. Kaplan-Meier cumulative hazard function of rupture. Five-year hazard estimates are illustrated for patients as a function of initial aneurysm size (p = 0.0045).

Table 7. Proportional Hazards Regression of Factors Predicting Increased Rates of Rupture[a]

Regression Analysis Variable	Conservative Model Variable Estimate	Entry at $p < 0.05$[b]			
		Standard Error	p Value	Odds Ratio[c]	
Initial aortic size					
5.0–5.9 cm	2.400770[e]	1.12039	0.0321[e]	11.032[e]	(1.227–99.156)
≥ 6.0 cm[d]	3.294935[d]	1.08300	0.0023[d]	26.976[d]	(3.229–225.334)

[a] This variable equals 1 if the patient incurred a rupture and 0 otherwise. [b] Criteria for assessing model fit, −2 Log L, without covariates, 112.877; with covariates, 103.063; χ^2 for covariates, 9.814 with two degrees of freedom ($p = 0.0074$). [c] 95% confidence intervals on odds ratios are given in parentheses. [d] Statistically significant at the 0.5% level. [e] Statistically significant at the 5% level.

Larger aneurysms are associated with decreased long-term survival ($p = 0.0039$). Overall, survival for all patients in the database was better for nondissected than for dissected aortas (Fig 7). Survival was better for the ascending than for the descending aorta (Fig 8). Figure 9 illustrates the long-term survival after presentation of patients treated medically versus those treated with elective or emergent operation. Elective operation restores a flat survival curve indistinguishable from that of the normal population.

Comment

Examining the natural history of TAAs is complicated by a number of issues specific to the disease, which make scientific assessments of risks difficult. Patients with large aneurysms or high rates of growth between imaging studies and those with significant symptoms are usually selected for surgical intervention. Those who are not selected for operation may have been excluded as surgical candidates because of significant comorbidities. Therefore, studies of risk factors for complications require large sample sizes. This is the first report from our center in which data are robust enough (1,383 years of patient follow-up before surgical intervention) to permit statistically valid calculation of yearly rates of rupture or other complications for aneurysms of different sizes. Growth rates in this population were consistent with previous estimates [12–14]. The mean aortic growth rate was 0.10 cm per year.

This study confirms that TAA is intrinsically a lethal disease and that aneurysm size has a profound impact on rupture, dissection, and death. We find that the mean rate of rupture or dissection is only 2% per year for small aneurysms, rises to 3% for aneurysms 5.0 to 5.9 cm, and jumps to 6.9% for aneurysms of 6.0 cm in diameter or greater. The risk of rupture alone is near zero for small aneurysms, rises to 1.7% per year for aneurysms 5.0 to 5.9 cm, and jumps to 3.6% per year for aneurysms of 6.0 cm in diameter or greater. The risk of rupture, dissection, or death from all causes is 6.5% at aneurysm size 5.0 to 5.9 cm and jumps to 14.1% per year for aneurysms of 6.0 cm or greater.

Even more striking, when using proportional hazards regression, the odds ratio for rupture indicates that the risk over time of incurring a rupture is more than 25 times higher in patients with aneurysms of 6.0 cm or greater than in those between 4.0 cm and 4.9 cm. Furthermore, even aneurysms in the 5.0-cm to 5.9-cm range are associated with a more than 11 times higher risk of rupture than those in the 4.0-cm to 4.9-cm range.

It is anticipated that these size-specific rates may be of use in counseling individual patients presenting for consideration of elective preemptive surgical extirpation of

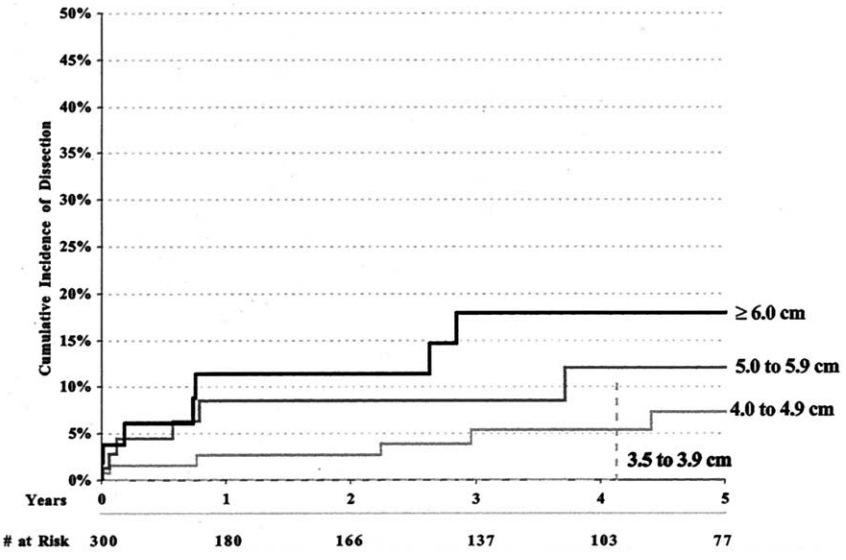

Fig 5. Kaplan-Meier cumulative hazard function of dissection. Five-year hazard estimates are illustrated for patients as a function of initial aneurysm size (p = *0.1878).*

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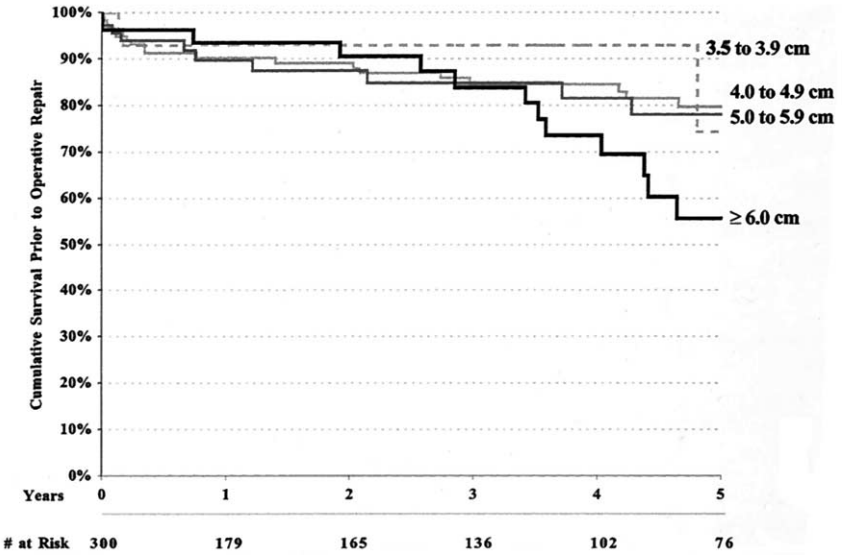

Fig 6. Kaplan-Meier cumulative survival before operative repair. Five-year survival estimates are illustrated for patients as a function of initial aneurysm size (p = 0.0671).

asymptomatic aneurysms. These data confirm that TAA is a highly lethal condition and support preemptive surgical correction. It is important to emphasize that these data are for asymptomatic aneurysms and that symptomatic aneurysms require extirpation regardless of size. The general thrust of these data suggests intervention before aneurysm size reaches 6.0 cm, consonant with findings and recommendations from our earlier report on a smaller number of patients [6]. Furthermore, these data indicate that aneurysms of smaller size (at least 5.0 cm) may also be associated with a high risk of complications. In fact, size appears to be the primary predictor of rupture.

For individual patients at specific centers, the center's surgical risk can be factored into the decision making. At our institution, for experienced surgeons, hospital mortality is 2.5% for elective ascending and arch and 10.9% for elective descending and thoracoabdominal aortic operations [8]. This indicates that surgical repair performed electively promises lifetime protection at a mortality cost comparable to, or less than, a single year's natural rupture or dissection rates. The very flat survival curve (Fig 9) after preemptive surgical repair approaches that of a normal age- and sex-matched population and confirms vividly that surgical repair protects life long-term.

Certain limitations of these data can be enumerated. Definition of rupture, dissection, and aneurysm-related death was strict, as we required in-hospital documentation by imaging studies, surgical findings, or postmortem examination. The true rate of rupture may be higher. The mortality calculations are immune from this factor and represent true rates. Second, patients we followed were operated on electively when they reached size criteria, thus eliminating them from susceptibility to rupture or dissection. The only patients with very large aneurysms followed without operation were those cared for else-

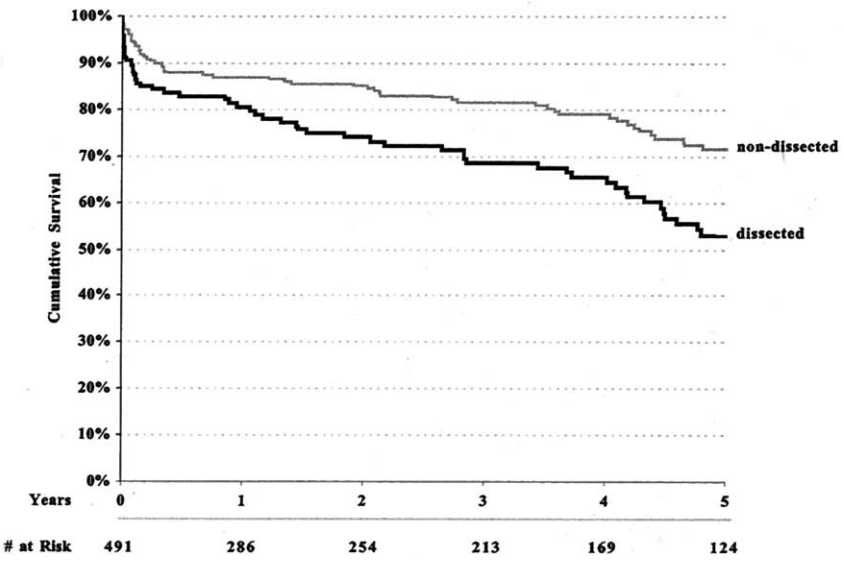

Fig 7. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of dissection status (p = 0.0002).

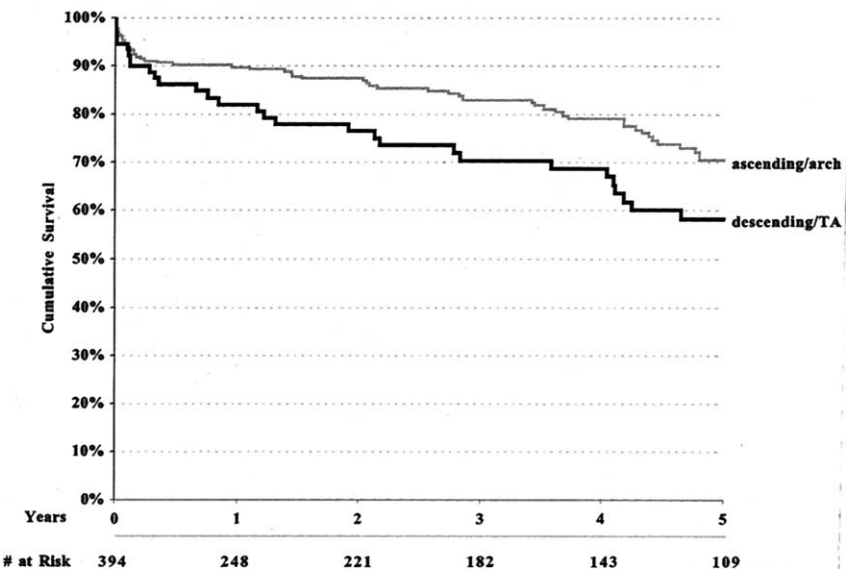

Fig 8. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of aneurysm location (p = 0.0023). (TA = thoracic aorta.)

where before referral to us, those refusing operation, or those believed to be nonsurgical candidates. These two factors—strict definition of aneurysm-related events, and limitation of patients at risk by preemptive operation—imply that the yearly rates we have presented represent minimum lower limits of the actual rates. Some out of hospital deaths were certainly aneurysm-related. Thus, in decision making and counseling, we can presume that the risk of rupture or dissection is at least 6.9% per year for 6-cm or greater aneurysms. On the other hand, the rupture rate cannot exceed the combined end point of 15.6%, as rupture is a lethal event or operatively corrected event.

Two interesting and unanticipated findings of our study are that comorbid vascular disease increased the risk of rupture (odds ratio greater than twofold) and that male sex provides some relative protection (odds ratio, 0.367). This suggests that women require closer scrutiny, possibly because a specific size aneurysm represents proportionately greater aortic dilatation in smaller patients of female sex. Another issue has to do with the influence of concomitant pulmonary disease on aortic events. Multiple prior studies have shown such correlation [9, 14, 15]. We found an adverse impact of pulmonary disease on the rate of growth of the aorta, but did not confirm an impact on rupture or dissection. Regarding hypertension, like the study by Juvonen and coworkers [9], we did not uncover a direct increase in rupture or dissection.

As would be expected, we found increasing size is more strongly associated with an increased risk of rupture, rather than an increased risk of dissection. Dissection may occur at smaller sizes because of other factors (such as connective tissue disease from Marfan syndrome or bicuspid aortic valve), whereas rupture appears to be a predominantly size-related event. This is supported by the fact that when rupture is analyzed alone using logistic regression techniques, size is the only

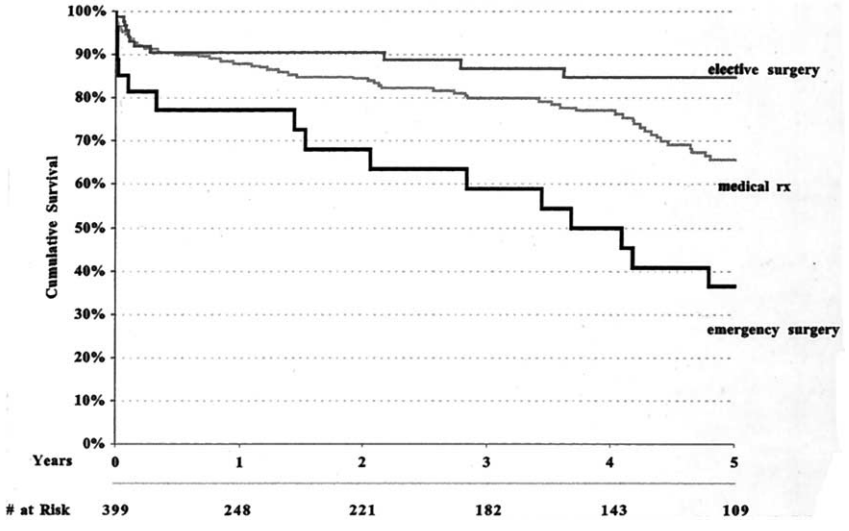

Fig 9. Kaplan-Meier cumulative survival. Five-year survival estimates are illustrated for patients as a function of presentation (p = 0.002). (rx = treatment.)

predictor of increasing risk (Table 7); however, when rupture and dissections were analyzed together (Table 5) male sex, a history of stroke, and the presence of Marfan disease all were predictive of higher complication rates.

This review of the natural history of TAAs before surgical repair permits the following conclusions. Thoracic aortic aneurysm is a lethal disease. Forty-six percent of patients with large aneurysms will die within 5 years. Aneurysm size has a profound impact on rupture, dissection, and death. The curves for each adverse event stack higher and higher above each other as aneurysm size increases. For counseling purposes, the patient with an aneurysm exceeding 6 cm in diameter can expect a yearly rate of rupture or dissection of at least 6.9% and a death rate of 15.6% per year. Elective operation eliminates the risk of rupture and restores survival to near normal. Elective surgical repair can be accomplished at a cost of less than a single year's expected natural mortality. Careful follow-up of patients with TAAs is essential, with preemptive extirpation before the dangerous diameter criterion of 6 cm. It is hoped that these data will permit concrete estimation of the natural history side of the balance of relative risks and benefits of medical management versus surgical intervention for specific patients.

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DISCUSSION

DR JOSEPH COSELLI (Houston, TX): We owe Dr Elefteriades and his colleagues a great deal of gratitude for their having established the aortic database at the Yale Center for Thoracic Aortic Disease. In a number of publications, this resource has provided us with information regarding guidelines as to when to intervene and operate on patients with thoracic aortic aneurysms, such as has been presented this morning. This particular study evaluates the risk of rupture, death, and the development of dissection in previously undissected aortas stratifying primarily for aortic size.

Operative intervention in the event of aortic rupture remains a devastating circumstance. Shown here, are the results of 1,611 patients upon whom we have operated for thoracoabdominal aortic aneurysms. Six percent (94 patients) were treated for rupture. The mortality and paraplegia/paraparesis were 17.6% (16 of 94 patients) and 21.2% (20 of 94 patients), clearly clinically significant ($p < 0.004$, $p < 0.007$, respectively). This is a slide of a patient with an 11 cm aortic aneurysm upon whom I operated upon last night in Houston for an extent IV thoracoabdominal aortic aneurysm and a contained leak. I am happy to report that she is doing fine.

I would like to ask the authors a few questions. They established, through analysis of their data, that the patients at reasonable risk with aneurysms of 6 cm or greater may be offered operation with less risk than continuing conservative medical management. Would it not be reasonable to operate when the aneurysm measures 5–6 cm as opposed to waiting until 6 cm or greater where the risk is so clearly definitive?

I found it of particular interest that the estimated annual growth rate for patients with pulmonary disease was equal to that of those with Marfan syndrome. I do not believe that this has previously been so clearly established. I would like the authors to comment upon the growth rate of specific size groupings and rate of enlargement with other important variables, such as hypertension, coronary artery disease, and abdominal aortic aneurysm. It is of interest that the authors have pointed out that the history of abdominal aortic aneurysm is a significant variable associated with dissection and rupture. The authors may want to comment upon whether or not this includes previous abdominal aortic aneurysm resection or abdominal aortic aneurysms followed clinically. I might add that our previous work has confirmed an increased incidence of thoracic aortic aneurysms in patients with abdominal aortic aneurysms. This presentation is the first report, of which I am aware, that associates a statistically increased risk of rupture and/or dissection.

I would like to thank the authors for their immense contribution to our knowledge in this field.

DR ELEFTERIADES: Thank you, Dr Coselli. You very appropriately called our attention to the issue of paraplegia as one of the costs of aortic operation. We did not include paraplegia in this discussion because of time. But one way that we look at the decision making for preemptive aortic operation is like refinancing one's mortgage. By operating on the aneurysm, one decreases the interest rate, or the rate of rupture in the future, but there are up-front closing costs, and the mortality of operation is only one of those up-front closing costs. Paraplegia for descending aneurysms is a very, very important additional closing cost, and we take that heavily into account. The yearly rates presented in this report can be brought down to an individual basis and the risk–benefit ratio calculated for a specific individual patient on the basis of his or her particular aneurysm. Fortunately, for ascending aneurysms, the decisions are easier because paraplegia is not an issue.

Your point about the pulmonary disease is an important one. I was speaking with Dr Griepp yesterday, and his group also found that pulmonary disease correlates with increased adverse aortic events. We were speculating together that we do not know which is the chicken and which is the egg—whether there is a common defect in connective tissues that affects both the lung and the aorta or whether there is something about the pulmonary disease that increases adverse events with the aneurysm.

Regarding the higher incidence of rupture in the setting of prior abdominal aortic aneurysm, we did find an odds ratio for rupture increased fourfold in patients with this history. This may be a marker for general severity of the aortic disease, but the number of patients in this subgroup is quite small, and this finding should be viewed as preliminary.

Your question about when we operate, at what size, is a very important one. We use 5.5 cm as our criterion for the ascending aorta; we use 6.5 cm for the descending, because of the corresponding observed sizes at the time of aortic events. We use a smaller size of 5 cm for the ascending aorta in patients with Marfan or those with a family history. When we take the aortic history in the office, it is impressive how often we get an affirmative response. We inquire, have you had any family members who died prematurely or suddenly or of unexpected cardiac death? The reply is positive very commonly. We consider patients with a family history or a suspected family history to have a connective tissue disorder, and we operate on them earlier, just like our patients with Marfan syndrome. So 5.5 cm is what we use without Marfan syndrome or a family history, and 5.0 cm for the ascending in case of Marfan syndrome or a positive family history.

Risk of Rupture or Dissection in Descending Thoracic Aortic Aneurysm

Joon Bum Kim, MD, PhD; Kibeom Kim, BA; Mark E. Lindsay, MD, PhD; Thomas MacGillivray, MD; Eric M. Isselbacher, MD; Richard P. Cambria, MD; Thoralf M. Sundt III, MD

Background—Current practice guidelines recommend surgical repair of large thoracic aortic aneurysms to prevent fatal aortic dissection or rupture, but limited natural history data exist to support clinical criteria for timely intervention.

Methods and Results—Of 3247 patients with thoracic aortic aneurysm registered in our institutional Thoracic Aortic Center Database, we identified and reviewed 257 nonsyndromic patients (age, 72.4±10.5 years; 143 female) with descending thoracic or thoracoabdominal aortic aneurysm without a history of aortic dissection in whom surgical intervention was not undertaken. The primary end point was a composite of aortic dissection/rupture and sudden death. Baseline mean maximal aortic diameter was 52.4±10.8 mm, with 103 patients having diameters ≥55 mm. During a median follow-up of 25.1 months (quartiles 1–3, 8.3–56.4 months), definite and possible aortic events occurred in 19 (7.4%) and 31 (12.1%) patients, respectively. On multivariable analyses, maximal aortic diameter at baseline emerged as the only significant predictor of aortic events (hazard ratio=1.12; 95% confidence interval, 1.08–1.15). Estimated rates of definite aortic events within 1 year were 5.5%, 7.2%, and 9.3% for aortic diameters of 50, 55, and 60 mm, respectively. Receiver-operating characteristic curves for discriminating aortic events were higher for indexed aortic sizes referenced by body size (area under the curve=0.832–0.889) but not significantly different from absolute maximal aortic diameter (area under the curve=0.805).

Conclusions—Aortic size was the principal factor related to aortic events in unrepaired descending thoracic or thoracoabdominal aortic aneurysm. Although the risk of aortic events started to increase with a diameter >5.0 to 5.5 cm, it is uncertain whether repair of thoracic aortic aneurysms in this range leads to overall benefit, and the threshold for repair requires further evaluation. **(*Circulation*. 2015;132:1620-1629. DOI: 10.1161/CIRCULATIONAHA.114.015177.)**

Key Words: aneurysm ■ aorta ■ prognosis ■ risk factors ■ surgery

Aneurysm of the descending thoracic (DTA) and thoracoabdominal aorta (TAA) is a life-threatening disorder given the risks of aortic dissection (AD) or rupture and their associated high mortality and morbidity once complications occur. The decision to intervene prophylactically, however, is complicated by the significant mortality and morbidity associated with surgical intervention for these conditions. Current practice guidelines call for surgical repair of asymptomatic thoracic aortic aneurysms with diameters of ≥55 mm as a Class I recommendation.[1] Extensive TAAs are given a higher threshold of 60 mm.[1]

Editorial see p 1600
Clinical Perspective on p 1629

Recent observations have shown that adverse aortic events may occur at smaller diameters.[2,3] For instance, reports from the International Registry of Acute Aortic Dissection showed that 40% of patients with acute type A AD may have aortic diameter of ≤50 mm, and among those with type B AD, as many as 80% had aortic diameters <55 mm.[3,4] These observations have encouraged re-examination of the current practice guidelines. Furthermore, progression of endovascular technology enables treatment of the aortic diseases less invasively, potentially reducing treatment-related mortality or serious morbidity.[5–9] Convergence of these forces suggests that earlier prophylactic interventions for DTAs may be appropriate and emphasizes the need for a deeper understanding of the predictors of these aortic complications. Finally, several aortic measures indexed to body size have been proposed recently as alternatives to simple diameter for predicting complications,[10,11] but few studies have examined the predictive value of these metrics.

Unfortunately, there are a number of significant challenges in determining the natural course of unrepaired TAAs,

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including the relatively uncommon population frequency of the condition, the incomplete nature of most data sets, and the problem of ascertaining causes of sudden death, not to mention the impact of censoring of data at the time of surgical intervention.[12] Much of our current understanding of the disease is based on the pioneering studies conducted by the group at Yale University, which is almost unique in the evaluation of the natural prognosis of unrepaired TAAs, and data from those studies stand as the only data of their kind cited in the current guidelines for indication of prophylactic aortic aneurysm repairs.[10,13,14] Despite their widespread use, these data have significant limitations, however. For instance, patients with and without connective tissue disease were included in the data set, and ascending versus descending thoracic aneurysms were not anatomically differentiated. A very sophisticated study was performed by Juvonen et al[15] to derive an equation to estimate rupture rate based on 114 patients with DTA/TAA aneurysms. However, the study was limited by a relatively small sample size and lack of consideration of the time effect in the statistical model.

We therefore sought to evaluate the outcomes of unrepaired descending thoracic and TAA aneurysms as captured in our institution's Thoracic Aortic Center database in the interest of contributing to a greater understanding of the optimal triggers for surgical intervention by determining independent predictors of adverse events.

Methods

Study Subjects

Patients with diverse aortic diseases referred to the Massachusetts General Hospital Thoracic Aortic Center are prospectively registered into an institutional database that records baseline patient characteristics, detailed information on aortic interventions, and follow-up outcomes. This database was queried for "thoracic aortic aneurysm" from July 1992 through August 2013, yielding 3247 adult patients (age ≥17 years). A retrospective review was then undertaken for these patients, including systematic reviews of computed tomography (CT) or magnetic resonance imaging (MRI) of the whole aorta performed at baseline. Aortic diameters were measured systematically at the levels of ascending, arch, descending thoracic, and thoracoabdominal segments. Patients with maximal aortic diameter of ≥35 mm were included in this study. In the interest of forming a more homogeneous study population with primary degenerative DTAs, those with known connective tissue disorders (Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes), inflammatory/neoplastic aortic diseases, AD, isolated ascending aortic aneurysm, history of prior thoracic aortic surgery, or congenital anomaly of the aorta (ie, coarctation of aorta and Kommerell diverticulum) were excluded. Patients scheduled to receive elective aortic interventions at the time of entry to the database were excluded (n=564: open surgery in 286, thoracic endovascular repair [TEVAR] in 278) because the course of dilated native aorta could not be evaluated. However, 1 patient scheduled for elective surgery had aortic rupture 19 days after initial presentation while awaiting operation; this patient was included in this study.

Most patients with aortic diameters of ≥55 mm, those demonstrating rapid expansion (>5 mm/y), or symptomatic patients with aneurysms underwent timely surgery during the study period; however, some of these patients refused surgery or were counseled against surgery related to comorbidities. Ultimately, 257 patients formed the study population, as shown in the flowchart for enrollment in Figure 1. When these patients were compared with 564 patients who were excluded because they underwent prompt surgery, the study group was significantly older (74.6±8.9 versus 70.1±9.9 years; P=0.001) and more frequently had chronic obstructive pulmonary disease (50.5% [52 of 103] versus 20.0% [113 of 564]; P<0.001).

Among the study patients, baseline CT or MRI images were reviewed for findings of atherosclerosis, mural calcification, and ulcer-like projection. The largest external diameter of the aorta was measured perpendicular to the axis of blood flow on the basis of baseline CT images or MRI.[1] In cases in which the aorta had elliptical cross-sectional shape, the smallest diameter was taken for the measurement, as previously reported.[16,17] Patients were designated as having aortic atherosclerosis if calcifications or luminal irregularity was identified in the aortic wall on these studies.

To evaluate the indexed aortic sizes relative to the body size, body surface area (BSA) was calculated based on the Du Bois formula (BSA=0.007148×weight$^{0.425}$×height$^{0.725}$),[18] and several indexes were calculated as follows: Yale index[10]=maximal aortic diameter (cm)/BSA (m^2); Svensson index[11]=maximal aortic cross-sectional area (cm^2)/height (m), and indexed area= maximal aortic cross-sectional area (cm^2)/BSA (m^2)

The study protocol was approved by the institutional review board, and the requirement for informed consent from individual patients was waived as a minimal-risk study owing to the retrospective nature of the study design.

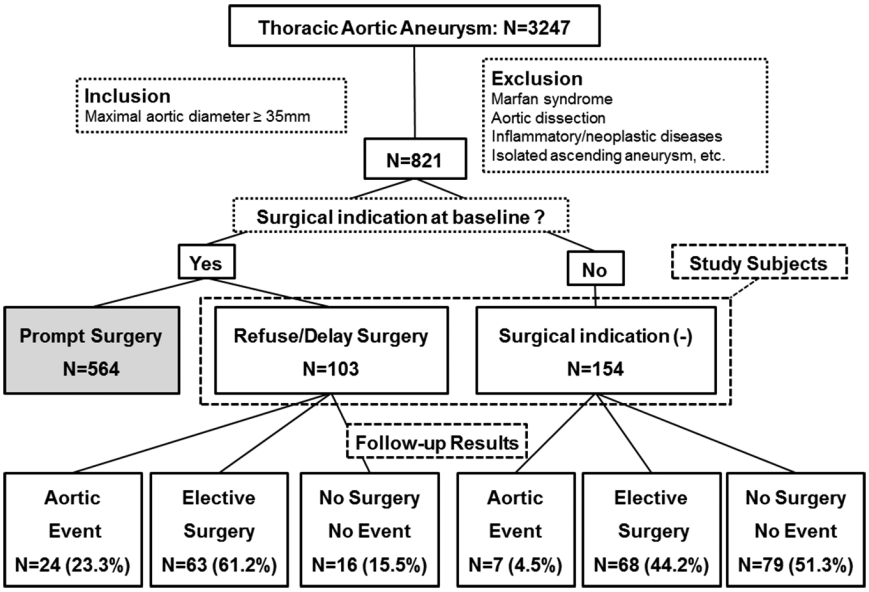

Figure 1. Flowchart for study enrollment and patient outcomes.

Definitions and Statistical Analysis

The primary end point was defined as a composite of adverse aortic events that included acute AD, aortic rupture, and sudden death not explained by causes other than aortic diseases. To establish unbiased definitions of the aortic events, we estimated aortic event rates as definite and possible events, as suggested by Lederle and colleagues.[19] Definite events were aortic rupture or AD as confirmed by adequate imaging studies (MRI or CT) or surgical findings. Possible events included, in addition to definite events, sudden unexplained or unwitnessed deaths. The true event rate was assumed to lie somewhere between the definite event rate and the possible event rate.

Because the primary aim of this study was to evaluate the natural course of unrepaired aortic aneurysm, patients who underwent elective aortic surgery before the aortic events or who died of causes other than aortic disease were regarded as censored at the time of such events.

Information on clinical end points of individual patient was obtained through August 2014 by a review of longitudinal data from Partners Health Care system. This system, the largest healthcare system in Massachusetts, maintains a centralized clinical data registry of all patient encounters.[20] Data on vital status and dates of death were further validated by the Social Security Death Index if necessary. Patients who were lost to follow-up were regarded as censored at the latest visit date if they had not had any adverse events up to that point.

SPSS software version 14.0 (SPSS Inc, an IBM company, Chicago, IL) and R statistical software version 3.1.2 were used for statistical analyses. Categorical variables are presented as frequencies and percentages, and continuous variables are expressed as mean±SD or median with range (or quartiles 1–3). Kaplan-Meier curves were plotted to display conditional probability of adverse aortic events, and log-rank tests were used to compare between-group differences in rates. For multivariable analyses, the Cox proportional hazards models were used to determine independent risk factors of adverse aortic events. Variables with a value of $P \leq 0.20$ in univariable analyses were candidates for the multivariable Cox models. Multivariable analyses involved a stepwise backward elimination technique, and only variables with a value of $P<0.10$ were used in the final model. To test the proportional hazards assumption in the Cox models, log (−log[survival]) curves were inspected, which confirmed no violation in the models.

The receiver-operating characteristic curve method was used to assess the predictability of baseline maximal aortic sizes for adverse aortic event within 1 year. This test was done for either absolute or relative aortic diameters indexed by body sizes. The results are presented by area under the curve with 95% confidence interval (CI) and were compared between absolute and each of indexed aortic diameters using the method suggested by DeLong et al.[21] Risks of aortic events within 1 year based on initial aortic diameter were estimated with the logistic regression models.

All reported P values were 2 sided, and a value of $P<0.05$ was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

For the baseline imaging of the aorta, CT was used in 237 patients, and 20 patients were evaluated with MRI. Table 1 summarizes baseline profiles of subject patients. As might be anticipated, most patients (>80%) had hypertension. A similar percentage had evidence of atherosclerosis in the aneurysmal aorta. Concomitant ascending aortic dilatation was observed in ≈60% of patients, most of which were <5.5 cm. About 60% of patients presented with aneurysms of the TAA, which was followed by DTA and arch in the descending frequencies. Distributions of maximal aortic diameter are illustrated in Figure 2, which shows differences in the distributions according to the location of the main aneurysmal lesions. At baseline, 103 patients (40.1%) demonstrated a diameter of ≥55 mm, with 62 patients (24.1%) having an aortic diameter of ≥60 mm. Data on height and weight were available for 196 (76.3%) to allow the calculation of indexed aortic sizes.

Clinical Outcomes

Follow-up was complete in 88.7% (n=228) with a median duration of 25.1 months (quartiles 1–3, 8.3–56.4 months, 791.5 patient-years). Figure 2 illustrates the outcomes

Table 1. Patient Characteristics at the Time of Presentation (n=257)

Age, y	72.4±10.5
Female sex, n (%)	143 (55.6)
Body mass index, kg/m²*	27.4±4.9
BSA, m²*	1.85±0.25
Diabetes mellitus, n (%)	34 (13.2)
Insulin therapy	3 (1.2)
No insulin therapy	31 (12.1)
Hypertension, n (%)	212 (82.5)
Chronic obstructive pulmonary disease, n (%)	105 (40.9)
Smoking history, n (%)	
Past	133 (51.8)
Current	51 (19.8)
Medications, n (%)	
β-Blockade	161 (62.6)
Calcium channel blockade	76 (29.6)
ACE inhibitor	84 (32.7)
Angiotensin receptor blocker	31 (12.1)
Diuretics	81 (31.5)
History of AAA surgery, n (%)	23 (8.9)
Main lesion location, n (%)	
Arch	23 (8.9)
Descending thoracic aorta	79 (30.7)
Thoracoabdominal aorta	155 (60.3)
Imaging findings	
Aortic sizes	
Maximal aortic diameter, mm	52.4±10.8
Yale index*	2.90±0.72
Svensson index*	13.2±5.8
Indexed area*†	12.3±5.5
Ulcer-like projection, n (%)	20 (7.8)
Atherosclerosis, n (%)	210 (81.7)
Calcification, n (%)	188 (73.2)
Concomitant ascending aorta dilatation ≥35 mm, n (%)	154 (59.9)
≥35–<40 mm	41 (16.0)
≥40–<50 mm	80 (31.1)
≥50 mm	33 (12.8)

AAA indicates infrarenal abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; and BSA, body surface area.

*Data available in 196 patients (76.3%).

†Indexed area=maximal aortic cross-sectional area (cm²)/ body surface area (m²).

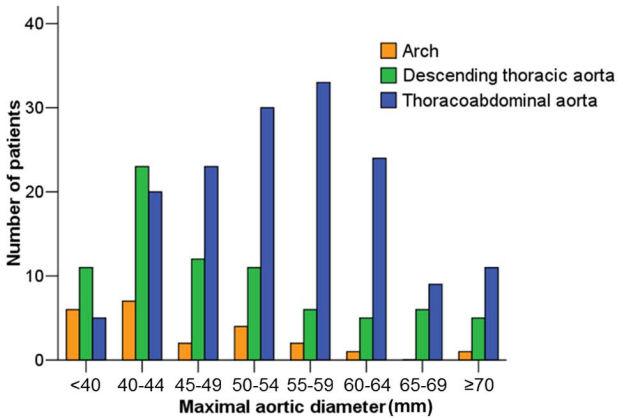

Figure 2. Distributions of maximal aortic diameters at baseline.

summary of patients. At baseline, 103 patients (40.1%) met conventional surgical indications based on aortic diameter (≥55 mm), but they refused surgery or delayed the decision to undergo surgery. In this patient group, 24 (23.3%) had aortic events during follow-up, of which 12 occurred within 1 year of initial presentation. Of these 24 patients, 10 patients underwent emergent operation (conventional open surgery in 4 and TEVAR in 6). Fatal outcome occurred in 15 of the 24 patients with aortic events (62.5%) including 1 patient who received emergent TEVAR. Another 63 of these patients (61.2%) underwent delayed elective aortic repair at a median of 7.1 months (range, 1.8–120 months) without experiencing interim aortic events. The final 16 patients with aortic diameter ≥5 mm at entry (15.5%) had been followed up for a median of 13.6 months (range, 2.7–71.6 months) and were free of adverse aortic events even without aortic intervention. Among these, 2 patients died of causes other than aortic disease at 26.9 and 58.0 months after the diagnosis of aortic aneurysm.

Among patients for whom surgery was not indicated at the initial presentation (n=154, 59.9%), 68 (44.1%) subsequently underwent elective aortic repair at a median of 34.8 months (range 3.4–155.7 months), most often because of progressive aortic dilatation (Figure 2). Another 7 patients (4.5%) in this group experienced adverse aortic events (rupture in 2, sudden death in 3, and AD in 2) at 3.2 to 141.2 months, of whom 4 had the events within 1 year of diagnosis. The remaining 79 patients remained alive (n=74) or died of other causes (n=5: cancer in 2, respiratory failure in 2 and multiple comorbidities in 1) without aortic intervention or an aortic event up to a median of 36.3 months (quartiles 1–3, 15.1–76.1 months).

Overall, 131 patients (60.0%) underwent elective aortic interventions (conventional open surgery in 74 and TEVAR in 57) at a median of 17.1 months (interquartile range, 5.9–38.4 months) with an operative mortality rate of 4.6% (n=6; TEVAR, 5.2% [3 of 57]; open surgery, 4.1% [3 of 74]), whereas the operative mortality rate among the 10 emergent cases was 10% (1 of 10, a TEVAR case).

Summary of Adverse Aortic Events

There were 19 definite and 31 possible adverse aortic events occurring at a median of 8.7 months (quartiles 1–3, 3.2–16.8 months; Table 2). Of these, 10 definite and 16 possible events occurred within 1 year after the diagnosis of aortic aneurysm. The adverse events were as follows: 4 cases of ADs, 15 cases of aortic rupture, and 12 sudden deaths. Locations of the 19 definite aortic events in patients who had rupture or dissection were as follows: arch in 1 (rupture), DTA in 7 (rupture in 6 and dissection in 1), and TAA in 11 (rupture in 8 and dissection in 3). The lesion locations were unidentified in 12 patients who died suddenly in whom the aneurysm had been located at the arch in 3 and TAA in 9.

Emergent aortic interventions were conducted for 10 patients with definite aortic events, including conventional open surgical TAA repair in 4 and TEVAR in 6. Fatal outcomes occurred in 9 of the 19 patients (47.4%) with definite aortic events, including 1 patient who underwent emergent TEVAR (mortality rate of emergent surgery, 10.0%).

Of 31 patients who had possible aortic events, 14 patients had interim CT assessments between the time of initial presentation and the time of aortic events (Table I in the online-only Data Supplement). Mean aortic expansion rate was 3.9 mm/y in these patients, and 3 patients showed rapid expansion of the aorta (>5 mm/y). In 4 patients whose aneurysms were <55 mm, follow-up CT scans showed aortic diameters >55 mm in all patients.

For the study group as a whole, regardless of aortic diameter, cumulative incidence rates at 1, 3, and 5 years were 4.3±1.3%, 6.9±1.9%, and 9.7±2.6%, respectively, for definite aortic events and 6.6±1.6%, 12.1±2.4%, and 16.5±3.1%, respectively, for possible events (Figure 3A). Both the definite and possible event rates were significantly different according to the baseline maximal aortic sizes. Figure 3B and 3C

Table 2. Patient Outcomes

	Total (n=257)
Definite adverse aortic event, n (%)*	19 (7.4)
Possible adverse aortic event, n (%)*	31 (12.1)
Rupture	15 (5.8)
Aortic dissection	4 (1.6)
Sudden death	12 (4.7)
Emergent surgery	10 (3.9)
Open TAA surgery	4 (1.6)
TEVAR	6 (2.3)
Fatal outcome by aortic events	19 (7.4)
Definite event within 1 y of diagnosis, n (%)*	10 (3.9)
Possible event within 1 y of diagnosis, n (%)*	16 (6.2)
Elective operation during follow-up, n (%)	141 (54.9)
Open TAA surgery	69 (26.8)
TEVAR	57 (22.2)
Arch repair	5 (1.9)
Death resulting from other causes, n (%)†	13 (5.1)

TAA indicates thoracoabdominal aorta; and TEVAR, thoracic endovascular aortic repair.

*Definite aortic events include aortic dissection and rupture; possible aortic events include sudden death in addition to definite aortic events.

†Cancer in 2 patients, respiratory causes in 2 patients, operative mortality after elective aortic repair in 6 patients, and multiple comorbidity in 3 patients.

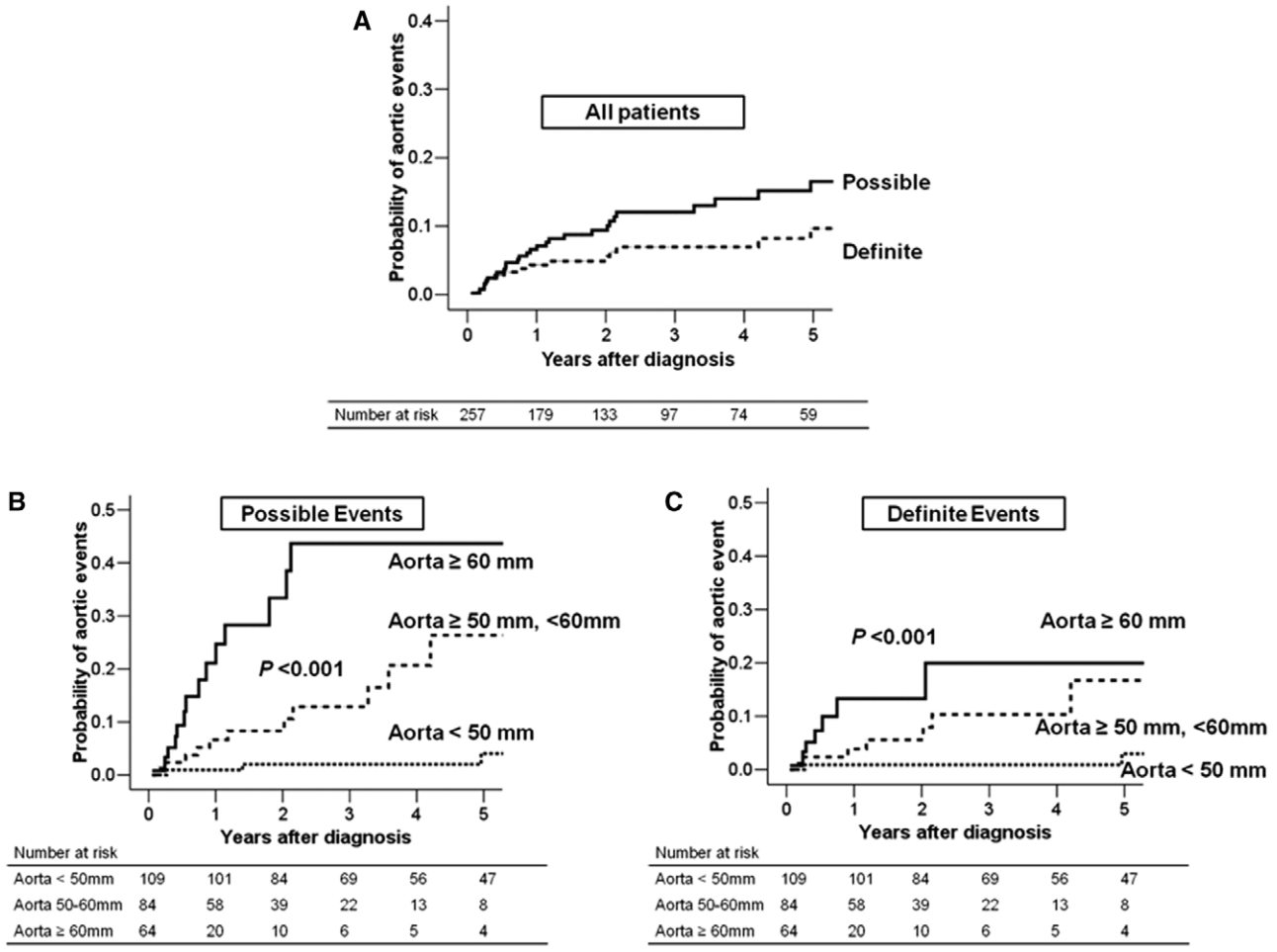

Figure 3. Cumulative risk of adverse aortic events overall (**A**) and possible (**B**) and definite (**C**) events stratified by initial maximal aortic diameter.

illustrates cumulative incidence rates of aortic events according to the maximal baseline aortic diameters, indicating significantly higher risks of adverse aortic events in larger aorta.

The probability of adverse aortic events within 1 year according to the baseline aortic diameters is illustrated in Figure 4. Patients with aortic diameter <50 mm experienced an event rate of <1%; however, the definite and possible event rates rose to 2.7% and 8.1% at aortic diameters between 50 and 60 mm and sharply increased thereafter at a rate of 37.5% to 62.5% at >70 mm.

Predictors of Adverse Aortic Events

Table 3 summarizes the univariable and multivariable risk factor analyses of the adverse aortic events. On multivariable analyses, maximal aortic diameter (hazard ratio, 1.10; 95% CI, 1.06–1.15; *P*<0.001) and the presence of chronic obstructive pulmonary disease (hazard ratio, 2.76; 95% CI, 1.04–7.32; *P*=0.042) emerged as significant independent predictors of the definite aortic events. When extended to the possible aortic events, baseline maximal aortic diameter was the only significant and independent risk factor (hazard ratio, 1.12; 95% CI, 1.08–1.15; *P*<0.001).

The receiver-operating characteristic curve method was used to assess the predictability of baseline maximal aortic sizes for adverse aortic event within 1 year (Table 4). The receiver-operating characteristic curve yielded an area under the curve of 0.852 (95% CI, 0.759–0.945; *P*<0.001) for possible events and 0.805 (95% CI, 0.604–1.006; *P*=0.012) for definite events. All of the relative aortic size indexes presented by the Yale index, the Svensson index, and the indexed area

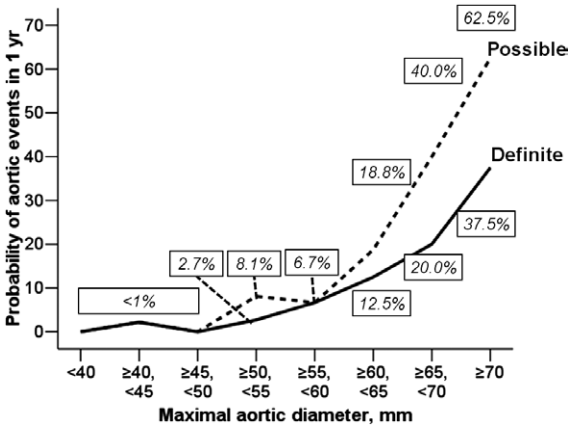

Figure 4. Observed proportions of definite and possible adverse aortic events within 1 year based on baseline maximal aortic diameter.

Table 3. Univariable and Multivariable Analyses for Adverse Aortic Events

		Univariable			Multivariable		
Type of Event	Risk Factors	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Definite	Age (by 1-y increment)	1.06	1.00–1.12	0.048			
	Female sex (vs male)	0.73	0.29–1.85	0.51			
	Diabetes mellitus	1.65	0.48–5.72	0.43			
	Hypertension	4.12	0.55–30.92	0.17			
	Current smoking	1.48	0.32–6.74	0.61			
	COPD	3.52	1.33–9.23	0.011	2.76	1.04–7.32	0.042
	Hypertension medications	…	…	0.24–0.99			
	Maximal aortic diameter (by 1-mm increment)	1.11	1.06–1.15	<0.001	1.10	1.06–1.15	<0.001
	Ulcer-like projection	0.05	0.01–385.34	0.50			
	Atherosclerosis	6.93	0.91–53.00	0.062			
	Calcification	1.72	0.60–4.94	0.32			
	Ascending aortic diameter	0.97	0.91–1.04	0.35			
Possible	Age (by 1-y increment)	1.07	1.02–1.12	0.004	1.04	0.99–1.09	0.12
	Female sex (vs male)	1.04	0.51–2.13	0.91			
	Diabetes mellitus	2.59	0.35–19.3	0.35			
	Hypertension	2.07	0.63–6.83	0.23			
	Current smoking	1.57	0.47–5.19	0.46			
	COPD	1.69	0.84–3.43	0.14			
	Hypertension medications	…	…	0.17–0.72			
	Maximal aortic diameter (by 1-mm increment)	1.12	1.09–1.16	<0.001	1.12	1.08–1.15	<0.001
	Ulcer-like projection	0.60	0.08–4.43	0.62			
	Atherosclerosis	5.12	1.21–21.74	0.027			
	Calcification	2.00	0.84–4.72	0.12			
	Ascending aortic diameter	0.95	0.90–1.01	0.086			

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; and HR, hazard ratio.

showed greater area under the curve and accuracy for both the possible and definite aortic events compared with the absolute aortic diameter (Table 4), but these differences were not statistically significant (P=0.14–0.31 for definite events and P=0.15–0.39 for possible events).

Estimation of Adverse Aortic Events Within 1 Year

Risks of aortic events within 1 year based on initial aortic diameter were estimated with the logistic regression models described in Figure 5 (top). Figure 5 also illustrates the estimated risk for varying initial aortic diameters. For these models, 200 patients who were followed up for >1 year from baseline or had aortic events (10 definite and 16 possible events) within 1 year were included. Maximal aortic diameter was the only independent factor of both definite and possible events; therefore, we included only the aortic diameter as an independent variable in the model. The estimated risks of definite aortic events were 5.5%, 7.2%, 9.3%, and 15.4% at aortic diameters of 50, 55, 60, and 70 mm, respectively. The estimated risks of possible aortic events were 8.0%, 11.2%, 15.6%, and 28.1% at aortic diameters of 50, 55, 60, and 70 mm, respectively. Similarly, the risks of aortic events based on indexed aortic dimensions are shown in Figure 5 (bottom). At indexed aortic dimension of 20.0,

Table 4. Receiver-Operating Characteristic Curve Methods for Baseline Size Indexes of the Aorta to Predict Adverse Aortic Events Within 1 Year

	Definite Aortic Events			Possible Aortic Events		
	AUC	95% CI	*P* Value	AUC	95% CI	*P* Value
Diameter	0.805	0.604–1.006	0.012	0.852	0.759–0.945	<0.001
Yale index	0.889	0.788–0.991	0.001	0.908	0.830–0.986	<0.001
Svensson index	0.832	0.654–1.010	0.006	0.874	0.734–1.014	<0.001
Indexed area*	0.874	0.743–1.006	0.002	0.905	0.803–1.008	<0.001

The P values are computed to test the null hypothesis that the AUC is from random prediction. AUC indicates area under the curve; and CI, confidence interval.

*Indexed area=maximal aortic cross-sectional area (cm^2)/ BSA (m^2).

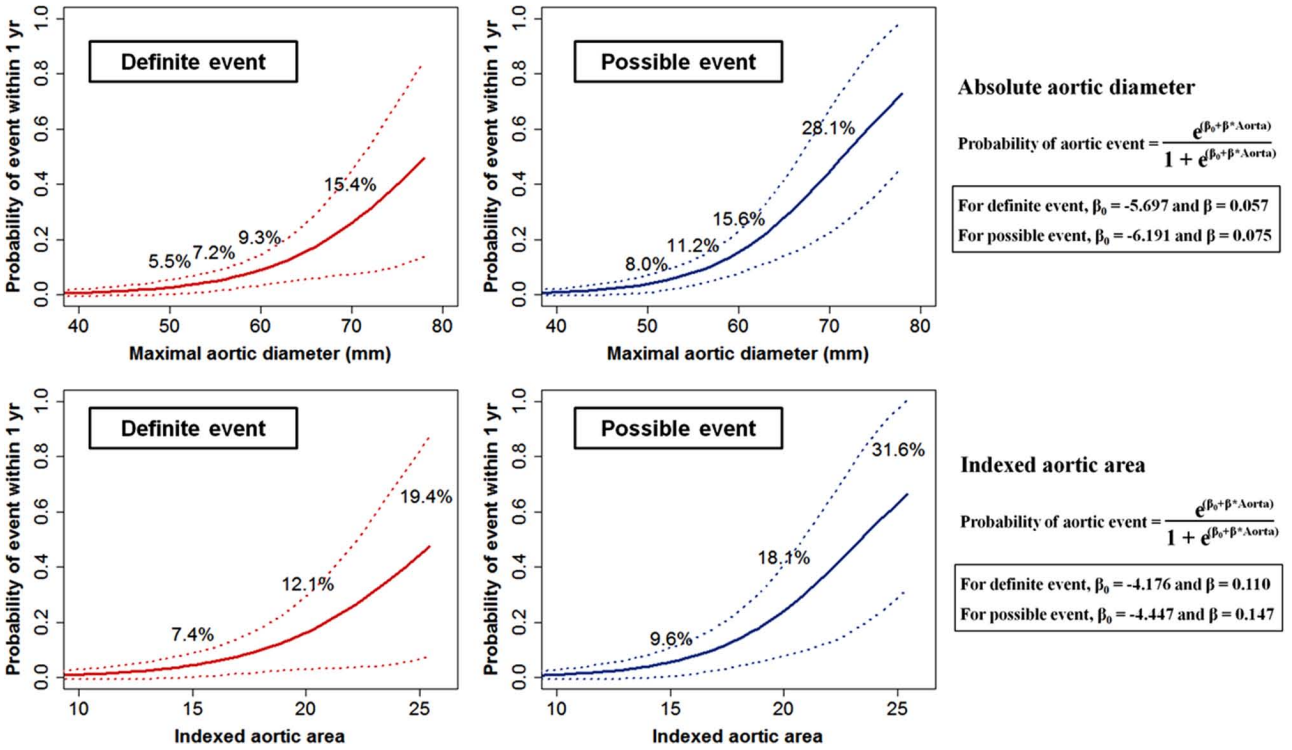

Figure 5. Predicted probability of aortic event within 1 year based on baseline aortic diameter (**top**) and aortic cross-sectional area indexed by body surface area (**bottom**) illustrated by logistic regression models. The dotted lines are 95% confidence bounds.

definite and possible aortic events are estimated as 12.1% and 18.1%, respectively.

Discussion

The current practice guidelines from the American College of Cardiology/American Heart Association recommend surgical or interventional aortic repair for symptomatic TAA regardless of the aneurysm size and prophylactic intervention for asymptomatic aneurysm when the aortic diameter reaches 55 to 60 mm or demonstrates rapid expansion (>5 mm/y).[1] The size criterion of 55 mm in the guidelines is derived principally from a series of pioneering studies conducted by a single research group.[10,13,14] In their 1997 study, Coady et al[13] evaluated 230 patients with TAA defined by the maximal aortic diameter of ≥35 mm. Those authors found that AD or rupture occurred in 32 patients during follow-up, mostly in the ascending aorta or arch (n=23). Logistic regression analyses revealed that baseline aortic diameter was the only significant risk factor for adverse aortic events, with a hinge point of aortic diameter of 60 mm.[5] From this result, the authors suggested prophylactic surgical aortic repair if the aortic diameter is ≥55 mm in patients without Marfan syndrome. In this study, however, the aneurysm locations were heterogeneous (ascending aorta in 111, its distal in 63), and the study population was mixed, including 25 patients with Marfan syndrome and patients with chronic dissection. Indeed, <50 patients without Marfan syndrome with degenerative DTAs or TAAs were evaluated in the cited study with <8 aortic events in this group. Two following studies from this research group were extensions of the original cohort and showed similar findings.[10,14]

Juvonen et al[15] conducted a prospective study to determine the prognosis of TAA. The study involved 114 patients with DTA/TAA aneurysms, for whom aortic sizes were measured systematically at the levels of descending thoracic aorta and abdominal aorta. During follow-up, 26 patients died of aortic rupture. On multivariable analyses, age, symptoms, COPD, and the diameters of DTA and abdominal aorta emerged as independent risk factors for rupture.. From these results, the authors suggested a piecewise exponential equation to estimate rupture rate that incorporated all the significant risk factors in the model. For instance, risks of aortic rupture in 65-year-old patients at a given aortic diameter are estimated as 5% at 5 cm, 9% at 6 cm, and 16% at 7 cm. From the study results, the authors concluded that balancing the risk of operation and the risk of rupture can be much more precise with the aid of an equation for the probability of rupture.

Despite the pioneering aspect of this study, a major assumption of the work was that the risk of rupture is constant and is not influenced by either the time after diagnosis or the length of time under surveillance. The lack of consideration of time under observation remains as a significant limitation of the analyses. In the present study, a predicted aortic events rate within 1 year can similarly be achieved by the logistic regression models, as shown in Figure 5. At a give baseline aortic diameter, the estimated risks of aortic events seem to be greater than those drawn by the formula suggested by Juvonen et al[15]; however, the discrepancies may be attributable to the differences in the study end points (death caused by rupture versus the composite of AD and rupture) and in the statistical methodologies.

The limitations of these pioneering studies led us to perform analyses on a larger, more homogeneous population of

DTA/TAA aneurysms patients to seek more optimal and anatomically specific information from which to develop surgical recommendations. In the present study, aortic rupture was the most frequent mode of definite adverse aortic events (15 of 19) in patients with DTA and TAA aneurysms, and the diameter of aorta was the only identifiable predictive factor. Furthermore, we observed a significant incidence of rupture of aneurysms below the conventional criteria, with >10% of patients with initial descending aortic diameter >52 mm experiencing aortic events within 1 year.

As is the case in any natural history study, some patients died of unknown causes. In this study, we have made an effort to account for the possibility that some aortic events may be missed among those suffering sudden unexplained or unwitnessed death by considering clinical events in definite or possible categories. This approach was used in a previous prospective, multicenter study of the incidence rupture in large abdominal aortic aneurysm among 198 patients with abdominal aortic aneurysm of ≥5.5 cm for whom elective abdominal aortic aneurysm repair was not planned because of medical contraindication or patient refusal.[19] In this study, abdominal aortic aneurysm rupture was categorized as definite, probable, or possible on the basis of ascertainment. The definite ruptures were those confirmed at surgery or autopsy or by CT. Probable ruptures included cases in which patients died with symptoms consistent with rupture but without objective confirmation of rupture. Possible ruptures included cases in which patients had sudden unexplained or unwitnessed deaths. Using this methodology, the authors assumed a true rupture rate to be somewhere in this range between definite and the possible rupture rates. By similar logic in the present study, the aortic event rates calculated ranged from 5.5% to 8.0% at 5-cm and from 9.3% to 15.6% at 6-cm baseline aortic diameter. In our study, as in the aforementioned study from Yale,[13] the study by Juvonen et al,[15] and the multicenter abdominal aortic aneurysm study,[19] patients followed up were declined or chose not to have surgery and accordingly were a selected subpopulation many of who likely had greater baseline comorbidities compared with those undergoing elective repair. Thus, some of the sudden unexplained deaths may likely be attributable to other reasons related to those comorbidities; therefore, "possible event" may overestimate the true risk of aortic events compared with expected. In this respect, the estimated risk for possible event should be interpreted with caution.

The aim of prophylactic surgery is to improve survival; however, one certainly trades short-term risk of the procedure for relief from later risk of rupture. The most meaningful outcome then is a comparison of overall survival between operated and nonoperated patients. We therefore evaluated overall survival outcomes in patients with an aortic diameter of ≥50 mm between the operated patients (564 patients who were excluded) and the nonoperated patients (subject patients). As might be anticipated, the survival rates in operated patients (564 patients who were excluded) did not differ according to the aortic sizes, but survival rates were significantly different in nonoperated patients (Figure I in the online-only Data Supplement). Compared with operated patients, survival rates of nonoperated patients were similar at 50 to 55 mm (P=0.74), but they were significantly poorer at 55 to 60 mm (P=0.035) and >60 mm (P<0.001). Although there is clearly significant selection bias inherent in our data set in the decision to undertake surgery, these figures may offer a crude idea about operative thresholds. In addition, when the cumulative incidences of aortic events are assessed by several groups divided by 5 mm in aortic diameters, there were tendencies of diverging prognosis at a 55-mm cutoff especially beyond the 2- to 3-year period for both definite and possible events (Figure II in the online-only Data Supplement), which may correlate better with the surgical threshold recommended by current practice guidelines. Thus, there may be value in looking at a group of patients with aortic diameters of 50 to 55 mm in further studies.

With the recognition that aortic size differs between individuals depending on body size, age, and sex[22,23] and with an appreciation for the limitations of simple aortic diameter, there has been interest of using indexed aortic size from a number of investigators. Of these factors, body size is the most dominant determinant. To account for these differences, Davies et al[10] introduced the aortic size index, which is the aortic diameter indexed by BSA and is now commonly known as the Yale index. In their evaluation of 410 patients with TAA aneurysm, the authors found that the Yale index better predicted the occurrence of rupture and death before operative repair than absolute diameter. From these observations, the authors recommended elective operative repair before the patient enters the zone of moderate risk (aortic size index >2.75 cm/m^2). Similarly, Svensson et al[11] introduced a different aortic size index, calculated by dividing the maximal aortic cross-sectional area by patient height and known as the Svensson index, to guide concomitant aortic repair during bicuspid aortic valve surgery. We used our data to test these indexed size parameters, and although we found the Yale index, Svensson index, and indexed cross-sectional area to have somewhat higher predictive values of ensuing aortic events than the absolute aortic diameter, this difference was not statistically significant.

Finally, the decision to proceed with surgery depends on the balance of the risks of surgery and the risk of observation.

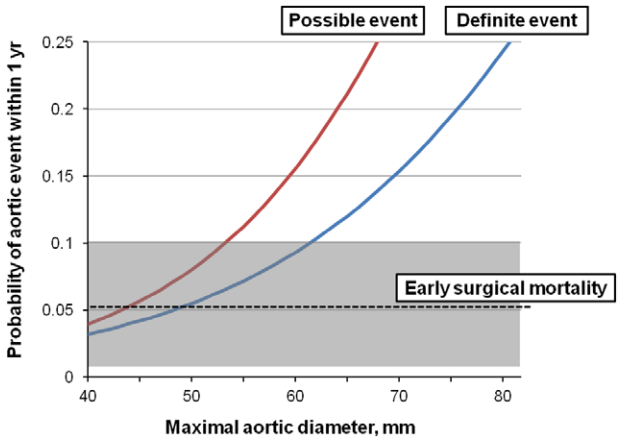

Figure 6. Risks of aortic events within 1 year based on initial aortic diameter vs early surgical mortality of elective thoracoabdominal aortic surgery. Elective surgical mortality in the current era ranges from 1.29% to 10.34% (grey zone) with the median rate of 5.06% (dotted line) according to a recent meta-analysis by Piazza and Ricotta.[24]

A previous meta-analysis of the operative risks of conventional open TAA repairs in the current era involving 27 studies and 7833 surgical patients undergoing open TAA repairs revealed a median early mortality rate of 5.06% (range, 1.29%–10.34%) and rates of permanent neurological damage of <5% under elective circumstances.[24] We therefore compared these surgical risks with aortic event rates within 1 year in Figure 6, suggesting that the risks of adverse aortic events exceed the average surgical mortality rate in the meta-analysis even at the aortic diameter of 50 mm. This comparison is imperfect given the fundamental differences in populations; that is, the nonoperative group was largely inoperable and the operated group was clearly selected. Nonetheless, the figure graphically demonstrates that elective surgical indications should be determined not only by aortic size but also on the basis of baseline patient risk profiles, the extent of aortic disease, and the institutional experience with DTA/TAA aneurysms repairs. The expected reduction in operative mortality and morbidity associated with TEVAR may further affect this balance.

In this study, for example, 46 patients had aortic diameters of 50 to 54 mm. During the study period, 667 patients showed aortic diameters of ≥55 mm; they were regarded as surgical candidates ("prompt surgery" [n=564] and "refuse/delay surgery" [n=103] in Figure 2). If we project the impact of lowering the surgical threshold to 50 mm, the number of surgical candidates would increase by 6.7% (46 of 667). Lowering the threshold for elective repair of TAAs would therefore have a significant economic impact on quite a large population. Therefore, a recommendation to extend the surgical criteria should have a robust foundation, perhaps based on a prospective, randomized trial, to test whether such extension gives more benefits to these patients. This has been done in the setting of infrarenal abdominal aortic aneurysms 4.0 to 5.5 cm in diameter in patients who were randomized to receive surgery or close observation. Interestingly, this study failed to show overall benefits of surgery in these patients, indicating that aneurysms should not be prophylactically repaired unless they are at least 5.5 cm in most circumstances.[25,26]

Limitations

This study has significant limitations, as do the similar prior studies on this subject. The data set represents the experience of a single tertiary academic referral center over 2 decades and thus is subject to referral (entry) bias from the community. This is even true within our institution, because, given its large size and scope, thoracic aortic aneurysmal disease is managed by members of several divisions and departments, and not all are entered into this specific Thoracic Aortic Center database. Furthermore, it is difficult to adequately account for the impact of surgical intervention, which clearly interrupts the natural history of the condition as it is intended, but is also affected by clinical judgments and secular trends beyond the actual behavior of the aorta. Indeed, in the current era, a true "natural history" study is not possible. Equally problematic, the study population includes many patients who did not undergo elective aortic repair because of serious comorbidities that may in themselves affect rupture rate, as suggested by Juvonen and colleagues.[15] These unoperated patients therefore may not be truly representative of usual patients with DTA/TAA aneurysms. The potential bias introduced by the selection of better-risk patients for surgery may have affected the results, with the nonoperated group faring worse than might be expected absent by surgical selection. Again, this shortcoming is one shared by the aforementioned studies on which current recommendations are based.[10,13–15,19] Nevertheless, these patients serve as the only available windows into the estimation of the prognosis of unrepaired aortic aneurysm. Finally, the main analyses of the study were based on 19 definite and 31 possible aortic events, which may be regarded as small numbers to generalize the study results. Therefore, studies on larger cohorts are needed to further verify the main findings of the present study.

Conclusions

Aortic diameter remains a predictor of aortic events in unrepaired DTA or TAA aneurysms. Importantly, even among patients with aortic diameters of 50 mm, 5.5% had definite and 8.0% had possible aortic events within 1 year. Consideration might therefore be given to lowering the threshold for intervention, particularly if less invasive endovascular approaches are feasible. Furthermore, these data suggest that relative aortic size may have an advantage in the prediction of adverse aortic events compared with absolute diameter alone.

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Disclosures

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CLINICAL PERSPECTIVE

Current practice guidelines recommend surgical repair of large thoracic aortic aneurysms to prevent fatal aortic dissection or rupture, but limited natural history data exist to support clinical criteria for timely intervention. In this study, we re-evaluated 257 nonsyndromic patients (age, 72.4±10.5 years; 143 female) with degenerative descending thoracic or thoracoabdominal aortic aneurysm in whom surgical intervention was not undertaken. During follow-up (791.5 patient-years), there were 19 definite (confirmed aortic dissection or rupture) and 31 possible (unexplained sudden deaths in addition to definite events) adverse aortic events. On multivariable analyses, maximal aortic diameter emerged as the only significant and independent risk factor for adverse aortic events (hazard ratio, 1.12; 95% confidence interval, 1.08–1.15; $P<0.001$). The estimated risks of aortic events within 1 year were 5.5% to 8.0%, 7.2% to 11.2%, 9.3% to 15.6%, and 15.4% to 28.1% at aortic diameters of 50, 55, 60, and 70 mm, respectively. In addition, receiver-operating characteristic curve analysis showed that indexed aortic sizes referenced by body sizes were more predictive of aortic events (area under curve=0.832–0.889) compared with absolute maximal aortic diameter (area under curve=0.805). Importantly, even among patients having an aortic diameter of 50 mm, 5.5% had definite and 8.0% had possible aortic events within 1 year. Consideration might therefore be given to lowering the threshold for intervention, particularly if less invasive endovascular approaches are feasible. Furthermore, these data suggest that relative aortic size may have an advantage in the prediction of adverse aortic events compared with absolute diameter alone.

Decision-making algorithm for ascending aortic aneurysm: Effectiveness in clinical application?

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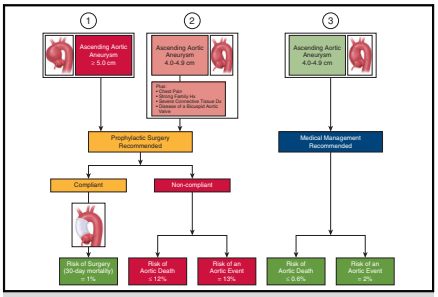
ABSTRACT

Objective: The risk of rupture and dissection in ascending thoracic aortic aneurysms increases as the aortic diameter exceeds 5 cm. This study evaluates the clinical effectiveness of a specific algorithm based on size and symptoms for preemptive surgery to prevent complications.

Methods: A total of 781 patients with nondissecting ascending thoracic aortic aneurysms who presented electively for evaluation to our institution from 2011 to 2017 were triaged to surgery (n = 607, 77%) or medical observation (n = 181, 24%) based on a specific algorithm: surgery for large (>5 cm) or symptomatic aneurysms. A total of 309 of 781 patients did not undergo surgery. Of these, 128 (16%) had been triaged to prompt repair but did not undergo surgery for a variety of reasons (''surgery noncompliant and overwhelming comorbidities'' group). Another 181 patients (24%) were triaged to medical management (''medical'' group).

Results: In the ''surgery noncompliant and overwhelming comorbidities'' versus the ''medical'' group, mean aortic diameters were 5 ± 0.5 cm versus 4.45 ± 0.4 cm and aortic events (rupture/dissection) occurred in 17 patients (13.3%) versus 3 patients (1.7%), respectively ($P < .001$). Later elective surgeries (representing late compliance in the ''surgery noncompliant and overwhelming comorbidities group'' or onset of growth or symptoms in the ''medical'' group) were conducted in 21 patients (16.4%) versus 15 patients (8.3%) ($P = .04$), respectively. Death ensued in 20 patients (15.6%) versus 6 patients (3.3%) ($P < .001$), respectively. In the ''surgery noncompliant and overwhelming comorbidities'' group, 7 of 20 patients died of definite aortic causes compared with none in the ''medical'' group.

Conclusions: Patients with ascending thoracic aortic aneurysms who did not follow surgical recommendations experienced substantially worse outcomes compared with medically triaged candidates. The specific algorithm based on size and symptoms functioned effectively in the clinical setting, correctly identifying both at-risk and safe patients. (J Thorac Cardiovasc Surg 2019;157:1733-45)



Schematic of the decision-making algorithm and main outcomes for each group of patients.

Central Message

A specific algorithm for triaging patients with ascending aortic aneurysms based on size and symptoms functioned effectively in the clinical setting, correctly identifying both at-risk and safe patients.

Perspective

Aortic diameter remains a powerful predictor of adverse aortic events and forms the basis of surgical intervention criteria that have been established for prophylactic repair of ascending aortic aneurysm. Chest pain is also an important indicator. This evaluation of decision making based on size and symptoms reveals accurate triage to preserve life and avoid unnecessary surgery.

See Commentaries on pages 1746 and 1748.

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Abbreviations and Acronyms

AD = aortic dissection
AHI = aortic height index
ASI = aortic size index
ATAA = ascending thoracic aortic aneurysm

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Ascending thoracic aortic aneurysms (ATAAs) are slowly progressive but life-threatening diseases because of the natural risk of complications if left unchecked. ATAAs can aptly be termed "silent killers,"[1] because aneurysms seldom produce symptoms until dreadful complications occur, namely, aortic dissection (AD), rupture, and death.

Several limitations can hinder the study of the natural history of unrepaired ATAAs, including the relative rarity of the condition, the impact of censoring data at the time of intervention (ie, selecting out patients before they die of their disease), and the difficulty in accurately ascertaining the causes of death in these patients (many of them are misclassified as "cardiac" causes). Reports of routine radiographic imaging of patients who had sudden cardiac death have shown that a significant number of these patients (a staggering 8.3%) had type A AD as the cause of death.[2,3]

In 1997, our group first reported on the natural history of the thoracic aorta, estimating growth rates and displaying diameter "hinge points" at which the risk of aortic rupture or dissection increased sharply.[4] Our subsequent studies, based on a larger number of patients, permitted more robust calculations that validated these dangerous diameters and

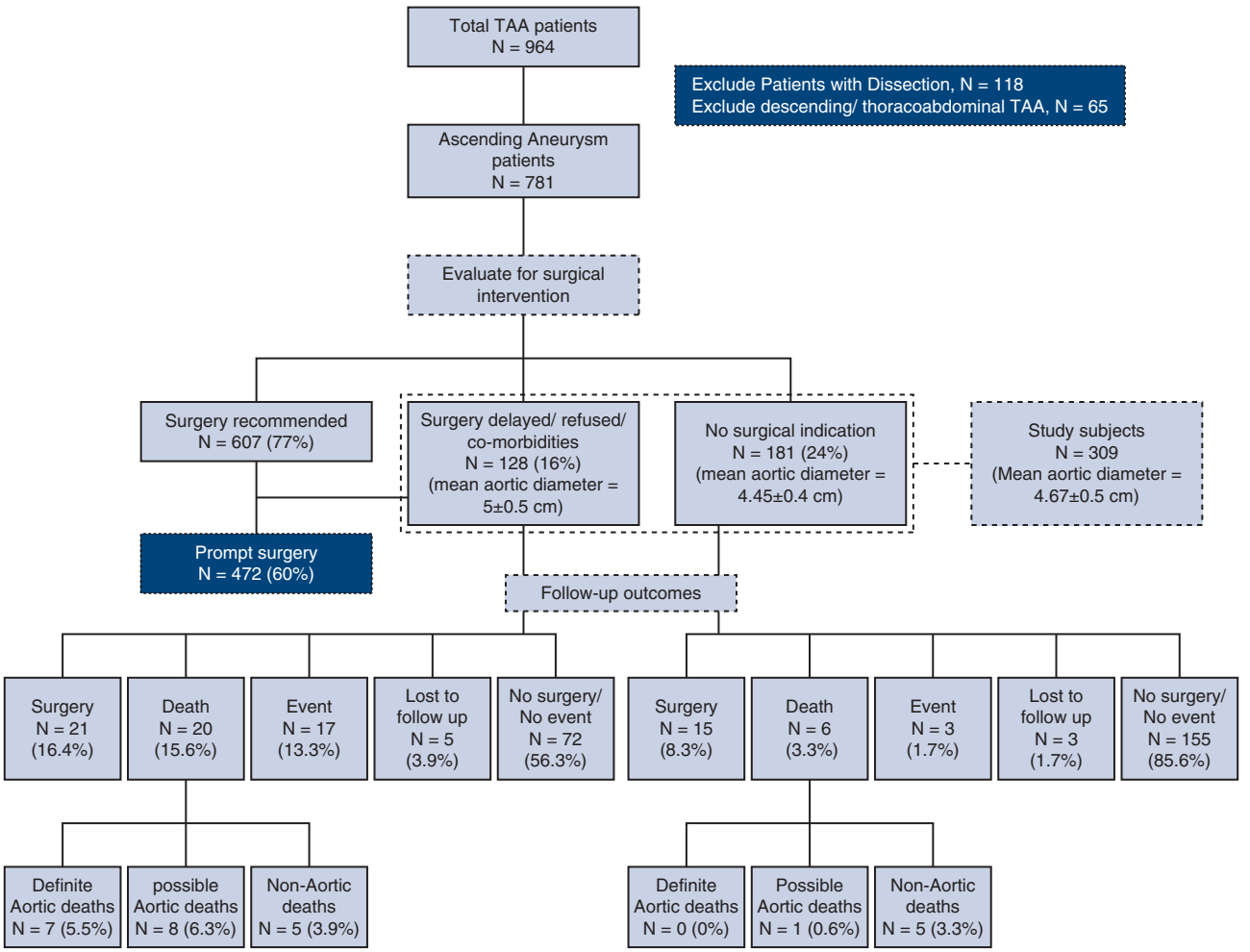


FIGURE 1. Flowchart for study patient triage and outcomes. *TAA*, Thoracic aortic aneurysm.

TABLE 1. Patient characteristics

Parameter*	Surgery "noncompliant and overwhelming comorbidities" group (n = 128)	Medical group (n = 181)	Chi-square	*P* value	Total (n = 309)
Age (y)	66.7 ± 13.6	67 ± 14	–	–	66.8 ± 13.8
Sex, n (%)					
Male	89 (69.5%)	132 (72.9%)	0.274	.6004	221 (71.5%)
Female	39 (30.5%)	49 (27.1%)	0.274	.6004	88 (28.5%)
Height (cm)	173.9 ± 10.6	175.4 ± 11.4	–	–	174.78 ± 11.07
Weight (kg)	87.5 ± 22.9	68.3 ± 22.6	–	–	86.77 ± 22.67
Body surface area (m^2)	2.04 ± 0.3	2.03 ± 0.3	–	–	2.03 ± 0.3
Body mass index (kg/m^2)	28.8 ± 6.12	27.7 ± 5	–	–	28.12 ± 5.53
Previous cardiac surgery, n (%)	13 (10.2%)	14 (7.7%)	0.289	.5906	27 (8.7%)
Coronary artery bypass grafting	10 (7.8%)	7 (3.9%)	1.55	.2132	17 (5.5%)
Aortic valve replacement	4 (3.1%)	7 (3.9%)	0.001	.9718	11 (3.6%)
Mitral valve replacement	1 (0.8%)	1 (0.6%)	0.061	.8049	2 (0.7%)
Imaging findings					
Main lesion location, n (%)					
Root	27 (21.1%)	35 (19.3%)	0.056	.8137	62 (20%)
Mid-ascending	95 (74.2%)	144 (79.6%)	0.934	.3338	239 (77.4%)
Arch	6 (4.7%)	2 (1.1%)	2.527	.1119	8 (2.6%)
Maximal diameter (cm)	5.0 ± 0.5	4.45 ± 0.5			4.67 ± 0.5
Aortic height index (cm/m)	2.9 ± 0.4	2.53 ± 0.21	–	–	2.67 ± 0.35
Aortic size index (cm/m^2)	2.2 ± 0.3	2.5 ± 0.5	–	–	2.33 ± 0.41
Measurement modality, n (%)					
Computed tomography	110 (85.9%)	140 (77.4%)	3.046	.0809	250 (80.9%)
Magnetic resonance imaging	6 (4.7%)	12 (6.6%)	0.222	.6373	18 (5.8%)
Echo	12 (9.4%)	29 (16%)	2.33	.1269	41 (12.3%)

*Continuous variables are presented as mean ± standard deviation.

proposed indexing aortic diameter to anthropometric measures to account for the size differences in these patients.[5-8] Current practice guidelines and recent analyses recommend preemptive surgical intervention at ascending aortic diameters greater than 5.5 cm and between 4 and 5 cm for various genetically effectuated aortopathies.[9-11]

The ultimate evaluation of a clinical triage algorithm is its clinical effectiveness in producing good clinical outcomes in the treatment limbs. In the present study, we evaluate the effectiveness of our algorithm for triaging ATAAs to surgery (aneurysm size ≥5 cm or a symptomatic aneurysm, ie, chest pain) or to medical management in patients not meeting these criteria.

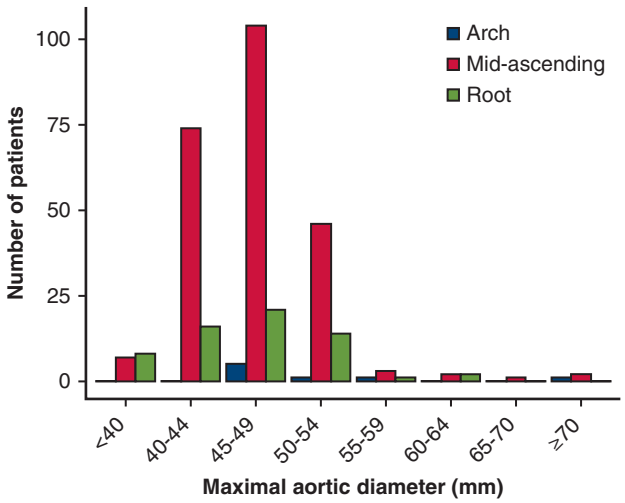


FIGURE 2. Distribution of maximal aortic diameters.

MATERIALS AND METHODS

Our database at the Aortic Institute at Yale-New Haven Hospital includes a total of 3455 patients with thoracic aortic disease. Of these, 964 consecutive patients presented electively for the first time to our institution (to author JAE) between January 2011 and February 2017. These patients form the basis for this study.

To constitute a homogenous study population, we excluded patients with concomitant descending or thoracoabdominal aneurysms and patients with chronic AD, traumatic aortic rupture, or significant associated congenital aortic malformations (eg, coarctation of aorta). We identified 781 patients with isolated ATAA who were triaged to surgical intervention or medical management by the senior author (JAE) based on a specific algorithm: surgery for large aortic diameters greater than 5 cm or for the presence of symptoms (chest pain unexplained by other causes). Other factors commonly contributing to the decision to perform surgery on patients

TABLE 2. Patients' risk factors

Parameter, n (%)	Surgery "noncompliant and overwhelming comorbidities" group (n = 128)	Medical group (n = 181)	Chi-square	*P* value	Total (n = 309)
Family history	47 (36.7%)	71 (39.2%)	0.108	.7428	118 (38.2%)
Proven	25 (19.5%)	48 (26.5%)	1.66	.1975	73 (23.6%)
Possible	22 (17.2%)	23 (12.7%)	0.876	.3492	45 (14.6%)
Connective tissue diseases					
Marfan syndrome	–	7 (3.9%)	–	–	7 (2.3%)
Ehlers–Danlos syndrome	–	1 (0.6%)	–	–	1 (0.3%)
Hypertension	77 (60.2%)	82 (45.3%)	6.04	.014*	159 (51.5%)
Chronic kidney disease	23 (18%)	8 (4.4%)	13.785	.0002*	31 (10%)
Atrial fibrillation	21 (16.4%)	29 (16%)	0.008	.928	50 (16.2%)
Dyslipidemia	45 (35.2%)	52 (28.7%)	1.155	.2825	97 (31.4%)
Coronary artery disease	35 (27.3%)	29 (16%)	5.183	.0228*	64 (20.7%)
Smoking	58 (45.3%)	71 (39.2%)	0.905	.3413	129 (41.8%)
Stroke	10 (7.8%)	6 (3.3%)	2.241	.1344	16 (5.2%)
Obstructive sleep apnea	13 (10.2%)	17 (9.4%)	1.711	.1909	30 (9.7%)
Obesity	44 (34.4%)	54 (29.9%)	0.520	.471	98 (31.7%)
Congestive heart failure	13 (10.2%)	10 (5.5%)	1.711	.1909	23 (7.4%)
Diabetes mellitus	11 (8.6%)	10 (5.5%)	0.683	.4086	21 (6.8%)
Malignancy	15 (11.7%)	33 (18.2%)	1.953	.1622	48 (15.5%)
Associated conditions					
Bicuspid aortic valve	16 (12.5%)	14 (7.7%)	1.437	.2307	30 (9.7%)
Bovine arch[23]	13 (10.2%)	12 (6.6%)	0.824	.3639	25 (8.1%)
Aberrant subclavian artery	2 (1.6%)	2 (1.1%)	0.123	.726	4 (1.3%)
Abdominal aortic aneurysm	8 (6.3%)	5 (2.8%)	1.48	.2237	13 (4.2%)
Intracranial aneurysms	2 (1.6%)	4 (2.2%)	0.165	.6845	6 (1.9%)
Inflammatory arteritis					
Giant cell arteritis	2 (1.6%)	3 (1.7%)	0.004	.948	5 (1.6%)
Takayasu arteritis	1 (0.8%)	1 (0.6%)	0.061	.8049	2 (0.7%)

*Statistically significant *P* value.

with diameters 4 to 5 cm included strong family history of aortic aneurysms and events,[6] presence of severe connective tissue disease,[9] or disease of a bicuspid aortic valve.

Patients who underwent prompt surgical repair within 3 months of initial presentation (n = 472, 60%) were excluded from further outcome analysis. Our main interest was in determining the outcome of unoperated patients triaged to medical or surgical management. Patients triaged to surgery who did not undergo surgery (because of patient refusal, insurance issues, or severe comorbidities) formed the "surgery noncompliant and overwhelming comorbidities group" (n = 128, 16%). The remaining patients, who from the start were recommended for medical management, constitute the "medical group" (n = 181, 24%). Ultimately, these 2 groups of patients (n = 309) formed the study population (Figure 1). Medical management consisted mainly of serial follow-up and blood pressure control. We did not routinely prescribe beta-blockers, angiotensin receptor blockers, statins, or other medications for the aneurysm itself.

Radiologic and clinical data were retrospectively accrued from the hospital's electronic medical records system. We used traditional measurements (from axial and coronal images), and not the often misleading Centerline measurements, in our aortic assessments of the patients in this study. Of the 309 study patients, 221 (71.5%) were male and 88 (28.5%) were female. Mean age at presentation was 66.7 ± 13.6 years. Patients' characteristics are listed in Table 1.

Primary end points for this study were eventual elective surgical repair, development of an aortic event (AD, rupture), or death. In the "medical group," eventual elective repair was performed in certain patients who over time developed significant aortic enlargement such that they reached the diameter threshold for surgical intervention or who developed symptoms. In the "surgery noncompliant and overwhelming comorbidities" group, surgery was ultimately performed in certain patients who changed their decision regarding surgery, had their comorbidities controlled, or developed aortic events.

Aortic events were classified as definite and possible, as suggested by Lederle and colleagues,[12] and were recorded in the 2 groups. Definite aortic events (n = 11, 3.6%) were defined as the development of aortic rupture or AD, confirmed by an imaging modality, surgical finding during operative repair, or documentation in the death certificate. Possible aortic events (n = 9, 2.9%) were ascribed to patients whose death certificates classified

TABLE 3. Logistic regression analyzing the decision to perform surgery

Variable	Estimate	Odds ratio	95% Confidence interval	*P* value*
Aortic diameter (cm)				
Intercept	−1.78	0.168	0.00712-1.58	.163
4-5 cm	2.21	9.16	1.6385-173.08	.0397*
≥5 cm	4.82	1.24E+02	19.24463-2480.9	.0000208*
Male sex	−0.507	0.603	0.33435-1.08	.0903
Age	−0.0171	0.983	0.96176-1	.122
Family History	0.359	1.43	0.81759-2.52	.211
Bicuspid aortic valve	0.515	1.67	0.67464-4.17	.265
Bovine arch	0.422	1.53	0.59212-3.88	.375
Aortic size index (cm/m^2)				
Intercept	0.1662	1.181	0.2417-5.884	.038
Aortic size index 2.1-3.0	1.0289	2.798	1.5359-5.259	.00101*
Aortic size index ≥3.0	4.5379	9.349E+01	15.3538-1836.884	.0000451*
Male sex	0.4395	1.552	0.8543-2.878	.155
Age	−0.0256	0.975	0.9533-0.996	.0214*
Family History	−0.014	0.986	0.5797-1.671	.959
Bicuspid aortic valve	−0.0066	0.993	0.4137-2.359	.988
Bovine arch	0.4486	1.566	0.6475-3.795	.315
Aortic height index (cm/m)				
Intercept	0.02169	1.022	0.175-5.917	.981
Aortic height index 2.4-3.1	1.817154	6.154	2.671-16.281	.0000668*
Aortic height index ≥3.1	6.086112	4.397+02	62.52-9305.261	.000000229*
Male sex	0.476626	1.611	0.87-3.06	.136
Age	−0.038305	0.962	0.939-0.985	.00157*
Family history	0.147699	1.159	0.669-2.005	.597
Bicuspid aortic valve	0.000273	1	0.406-2.439	1
Bovine arch	0.370199	1.448	0.59-3.566	.415

*Statistically significant *P* value.

their cause of death as "cardiac" without specifying the precise cause. One patient died at an outside hospital, and the partner was informed that the cause of death was "aortic"; this patient was included in the "definite events" category.

Survival follow-up of patients was performed according to the Yale Aortic Institute Methodology described previously[13] through October 2017. Follow-up was complete in 301 patients (97.4%), with a mean follow-up of 38.9 ± 23 months. Data on the vital status and causes of death were further validated by obtaining death certificates from the State Vital Records Office at the Connecticut Department of Public Health to confirm the causes of death. For living patients who did not follow up with our center, efforts were made to obtain recent medical records from their referring physicians and primary care providers. In patients who were lost to follow-up (n = 8, 2.6%), the follow-up period for analysis ended upon their last clinical encounter.

Family history was considered positive if a relative of the patient had a thoracic aortic aneurysm or AD, confirmed on an imaging study, intraoperatively, or on autopsy, including affected relatives alive or who died. For statistical analysis, we used only patients with proven family history. The study was approved by the Human Investigation Committee of the Yale University School of Medicine.

Statistical Methods

Statistical analysis was performed using R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).[14] Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as values and percentages. The "zero time" (when the follow-up clock is started) is the time of the initial evaluation. Kaplan–Meier curves were used to display the survival probability in both groups, and log-rank test was used to determine the significance of outcome differences. Cumulative risks for definite, possible, and total events were plotted over the follow-up period and were stratified by maximal aortic diameter.

Cox-proportional hazards regression models were used to conduct multivariate analysis for aortic events, and logistic regression models were used to obtain odds ratios for the factors affecting decision-making.

The receiver operating characteristic method was used to assess the ability of the maximal aortic diameter to predict adverse aortic events within 1 year.[15] Absolute aortic diameter and indexed diameters (aortic size index [ASI]/aortic height index [AHI]) were evaluated.

RESULTS

Patients' Characteristics

Data on the location and maximal aortic diameters were obtained using computed tomography in 250 patients (80.9%), magnetic resonance imaging in 18 patients (5.8%), and transthoracic echocardiography/transesophageal echocardiography in 41 patients (12.3%). The location of maximal aortic diameter in the majority of patients was in the mid-ascending portion (n = 239, 77.4%) in comparison with the root (n = 62, 20%) and the proximal aortic arch (n = 8, 2.6%). The distribution of maximal aortic

TABLE 4. Patient outcomes

Outcome, n (%)	Surgery "noncompliant and overwhelming comorbidities" group	Medical group	Chi-square	*P* value	Total (n = 309)
Eventual repair	21 (16.4%)	15 (8.3%)	4.045	.0443*	36 (11.7%)
Mean diameter at time of repair	4.9 ± 1.1	4.8 ± 0.2	–	–	4.9 ± 0.7
Size increased	–	10 (5.5%)			–
Symptoms developed	–	5 (2.8%)			–
Inoperable	44 (34.4%)	–			–
Refusal of surgery	79 (61.7%)	–			–
Lost to follow-up	5 (3.9%)	3 (1.7%)	0.744	.3884	8 (2.6%)
Death	20 (15.6%)	6 (3.3%)	13.19	.0003*	26 (8.4%)
Aortic	7 (5.5%)	0 (0%)			7 (2.3%)
Possible aortic	8 (6.3%)	1 (0.6%)	8.087	.0045*	9 (2.9%)
Nonaortic	5 (3.9%)	5 (2.8%)	0.3132	.575693	10 (3.2%)
Aortic event	17 (13.3%)	3 (1.7%)	14.87	.0001*	20 (6.5%)
Definite	9 (7%)	2 (1.1%)	4.801	.0284*	11 (3.6%)
Possible	8 (6.3%)	1 (0.6%)	8.087	.0045*	9 (2.9%)
No surgery/no event	72 (56.3%)	155 (85.6%)	31.720	<.0001*	227 (73.5%)

*Statistically significant *P* value.

diameters is depicted in Figure 2, with most patients in the 4.5 to 5 cm category.

Analysis of the patients' risk factors (Table 2) showed that a large proportion of our cohort were smokers and hypertensive (51.5% and 41.8%, respectively), whereas diabetes mellitus was observed in only 21 patients (6.8%), consistent with previous observations.[16]

Compared with patients in the medical group, patients in the surgery noncompliant and overwhelming comorbidities group suffered more from hypertension (60.2% vs 45.3%, $P = .01$), chronic kidney disease (18% vs 4,4%, $P < .001$), and coronary artery disease (27.3% vs 16%, $P = .02$). A significant number of patients had a positive or a likely family history (38%), in line with the concept that thoracic

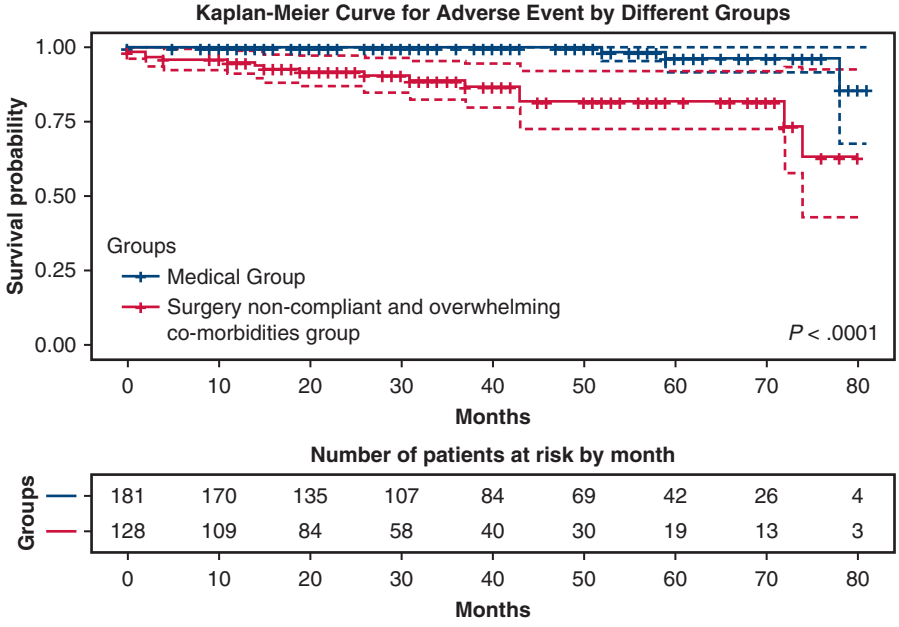


FIGURE 3. Kaplan–Meier curve for adverse events in surgical and medical groups.

aortic aneurysms exhibit a strong familial aggregation pattern.[17-19]

Triaging Algorithm

Logistic regression of the triaging algorithm was used to examine the effects of patient characteristics on the decision making, analyzing the factors that raise the odds of patients being triaged to surgery (Table 3). Analysis of the model confirmed the importance of the maximal aortic diameter on treatment choice, showing that patients were more likely to be selected for surgery in the group with aortic diameters 5.0 cm or greater compared with patients with aortic diameters less than 4.0 cm ($P < .001$). This analysis provides confirmation that the algorithm was applied as intended.

By indexing the aortic diameter to body habitus, similar models were constructed using the ASI and AHI. Compared with patients who were in the ASI categories less than 2.1 cm/m^2, patients were more likely to be selected for surgery in categories 2.1 to 3.0 cm/m^2 ($P = .001$) and 3.0 cm/m^2 or more ($P < .001$). Similar results were obtained by using the AHI, with patients in groups 2.4 to 3.1 cm/m and 3.1 cm/m or more being more likely to be selected for surgery, compared with patients who were in AHI categories less than 2.4 cm/m ($P < .001$). As might be anticipated, patients with older age were less likely to be selected for surgery, as depicted in the last model using the AHI ($P = .001$).

Outcomes

Significant differences in outcomes were found between the "surgery noncompliant and overwhelming comorbidities" group and the "medical" group in terms of aortic events (17 vs 3, $P < .001$), eventual repair (21 vs 15, $P = .04$), and death (20 vs 6, $P < .001$). In patients who underwent prompt surgery, hospital mortality occurred in 5 of 472 patients (1%), and postdischarge all-cause mortality occurred in 16 patients (3.4%). The mean follow-up in the 2 groups is similar ("noncompliant and overwhelming comorbidities" group 34.6 months, "medical" group 42 months). A summary of patient outcomes is outlined in (Table 4).

- Surgery noncompliant and overwhelming comorbidities group

  Of the total cohort, 128 patients (16%) met the surgical intervention criteria, based on symptoms and aortic diameter, but they refused surgery (n = 79, 61.72%) or were inoperable at that time (n = 44, 34.38%), constituting the "surgery noncompliant and overwhelming comorbidities group." Among the 44 patients who were "inoperable," 10 patients (7.8%) had severe comorbidities that hindered the

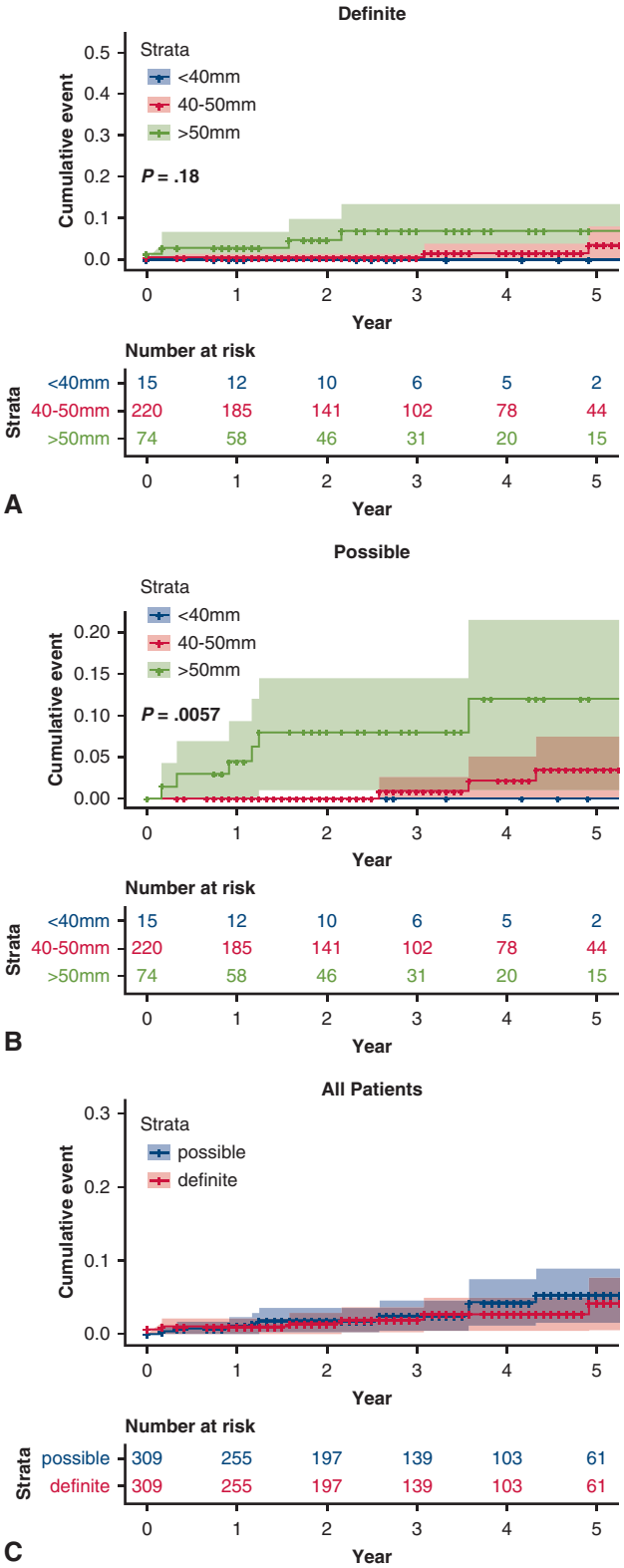


FIGURE 4. Cumulative risk of adverse events: definite (A), possible (B) "stratified by maximum aortic diameter," and all events (C). Confidence intervals are depicted by the shaded areas.

TABLE 5. Cox proportional hazard regressions on adverse aortic events

Type of event	Variable	Coefficient	Hazard ratio (95% confidence interval)	*P* value*
Definite (n = 11)				
	Maximal diameter	0.518	1.68 (0.92168-3.057)	.0904
	Age	−5.92E-03	0.994 (0.94522-1.046)	.8179
	Male sex	−1.31	0.271 (0.07044-1.044)	.0578
	Chronic kidney disease	0.897	2.45 (0.46596-12.896)	.2898
	Stroke	−0.0183	1.14E-08 (1.0638-19.507)	.9986
	Coronary artery disease	0.0822	1.09 (0.21201-5.56)	.9214
	Hypertension	0.688	1.99 (0.43683-9.054)	.374
Possible (n = 9)				
	Maximal diameter	1.09151	2.97876 (1.6439-5.398)	.00032*
	Age	0.01073	1.01079 (0.9508-1.075)	.73111
	Male sex	−0.25848	0.77222 (0.1535-3.884)	.75381
	Chronic kidney disease	1.51631	4.55537 (1.0638-19.507)	.04103*
	Stroke	1.788	5.97746 (1.001-35.694)	.04987
	Coronary artery disease	1.49423	4.45591 (0.9391-21.143)	.05999
	Hypertension	0.52855	1.69647 (0.2299-12.517)	.60422
Total events (n = 20)				
	Maximal diameter	0.784485	2.191277 (1.4436-3.326)	.000229*
	Age	−0.003316	0.996689 (0.9586-1.036)	.867551
	Male sex	−0.895619	0.408355 (0.1548-1.077)	.070261
	Chronic kidney disease	1.127614	3.088279 (1.0575-9.019)	.039184*
	Stroke	0.715267	2.044733 (0.4376-9.554)	.363177
	Coronary artery disease	0.86051	2.364367 (0.7965-7.018)	.121105
	Hypertension	0.560792	1.752059 (0.5326-5.763)	.355972

*Statistically significant *P* value.

decision for surgery, and 15 patients (11.7%) were aged more than 80 years and chose to continue with medical management rather than surgery. Nine patients (7%) were referred for bariatric surgery before aortic repair because of extreme obesity; however, they did not go through with it, and 10 patients (7.8%) had active treatments for cancer or human immunodeficiency virus that required completion before surgical aortic repair.

In this group, mean aortic diameter was 5 ± 0.5 cm. Thirteen patients (10.1%) had aortic diameters 5.5 cm or greater, and 74 patients (57.8%) had aortic diameters 5 cm or greater. Seventeen patients (21.76%) developed aortic events (9 definite and 8 possible), of which 15 events (88.2%) were fatal and 6 events (35.2%) occurred within 1 year of presentation.

Eventual aortic repair was carried out in 21 cases (16.4%), in patients who changed their mind regarding surgery (n = 12, 75.1%), had their comorbidities controlled (n = 7, 33.3%), or developed aortic events (AD) (n = 2, 9.5%).

Twenty patients (15.6%) died, of whom 7 (5.5%) had confirmed aortic deaths (3 ADs, 4 aortic ruptures), 8 patients (6.3%) had possible aortic deaths, and 5 patients (3.9%) had confirmed nonaortic deaths (2 myocardial infarctions, 1 aspiration pneumonia, 1 ruptured appendix and septicemia, and 1 cardiogenic shock).

Five patients (3.9%) were lost to follow-up, and only 72 patients (56.3%) had a benign course of follow-up, free of aortic events, aortic surgical intervention, or death.

- Medical management group

In the medical management group (n = 181, 24%), mean aortic diameter was smaller (4.45 ± 0.4 cm). Three patients (1.7%) developed aortic events (2 ADs and 1 possible event in the death certificate), none of which occurred within

TABLE 6. Receiver operating curve for baseline size indices of the aorta to predict adverse aortic events within 1 year

	Definite aortic events			Possible aortic events		
	AUC	95% CI	*P* value	AUC	95% CI	*P* value
Diameter	0.8355	0.7245-0.9465	.0226*	0.9831	0.9630-1.0000	.0019*
ASI	0.5169	0.0525-0.9136	.4611	0.8772	0.6392-1.0000	.0124*
AHI	0.8166	0.6735-0.9597	.0298*	0.9291	0.7245-1.0000	.0053*

AUC, Area under the curve; *CI,* confidence interval; *ASI,* aortic size index; *AHI,* aortic height index. *Statistically significant *P* value.

the first year. Six patients died, none of whom had a confirmed aortic death. Five patients had a confirmed nonaortic death (1 heart failure exacerbation, 1 chronic obstructive pulmonary disease exacerbation, 1 cerebral hemorrhage, 1 septic shock, and 1 metastatic bladder cancer), and 1 patient had a possible aortic death listed on the death certificate. Eventual elective repair was performed in patients whose aortic diameter enlarged significantly, meeting the surgical criterion (n = 10, 5.5%), or who developed symptoms (n = 5, 2.8%). Three patients (1.7%) were lost to follow-up, and the majority of patients (n = 155, 85.6%) continued to do well, neither requiring surgery nor experiencing any aortic events.

Kaplan–Meier survival analysis for adverse events (death, aortic events, repair) in both groups is depicted in Figure 3. The curve shows that survival probability was significantly better in the "medical" group throughout the whole follow-up period, compared with the surgery noncompliant and overwhelming comorbidities group ($P < .001$).

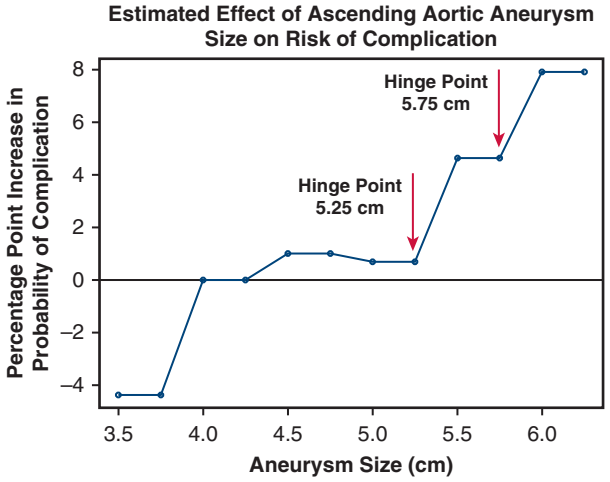


FIGURE 5. Estimated probability of rupture or dissection of the ascending aorta by aneurysm size, based on previous data from our group. Reprinted with permission from Zafar et al.[8]

Aortic Events

Overall, 20 patients experienced aortic events, 11 definite and 9 possible. Of these, 11 patients were female and 9 were male. The risk of adverse aortic events is depicted in Figure 4, showing an increased cumulative risk of events in patients with maximal aortic diameters greater than 5 cm, at 1, 3, and 5 years.

- Surgery noncompliant and overwhelming comorbidities group

  In the surgery noncompliant and overwhelming comorbidities group, definite aortic events occurred in 9 patients (5 type A ADs and 4 aortic ruptures) at a mean duration of 14 ± 13 months. Mean aortic diameter in the definite event group was 5.2 ± 0.57 cm. Five events occurred within 12 months of the first encounter, and aortic events were fatal in 7 patients. The remaining 2 patients underwent emergency repair for acute type-A AD and continued to do well during the follow-up.

  Eight patients had possible aortic events at a mean duration of 20 ± 16 months, all of whom died. Mean aortic diameter in patients with possible events was 5.7 ± 0.4 cm. Three events occurred within 12 months of the first encounter. All patients had a cardiac cause of death on the death certificate.

- Medical management group

  In the "medical" group, 2 patients developed AD (1 type A and 1 type B, both managed surgically, and continued to do well during the follow-up). One patient had a cardiac death listed on his death certificate and was classified as a possible aortic death. The mean maximal aortic diameter in these patients was 4.5 ± 0.4 cm, and events occurred at a mean duration of 34 ± 20 months.

Multivariable regression analysis of the total aortic events (Table 5) showed that the maximum aortic diameter was significantly associated with a higher risk of developing an event (hazard ratio, 2.19; $P < .001$). Higher risk was also observed in patients with chronic kidney disease (hazard ratio, 3; $P = .03$).

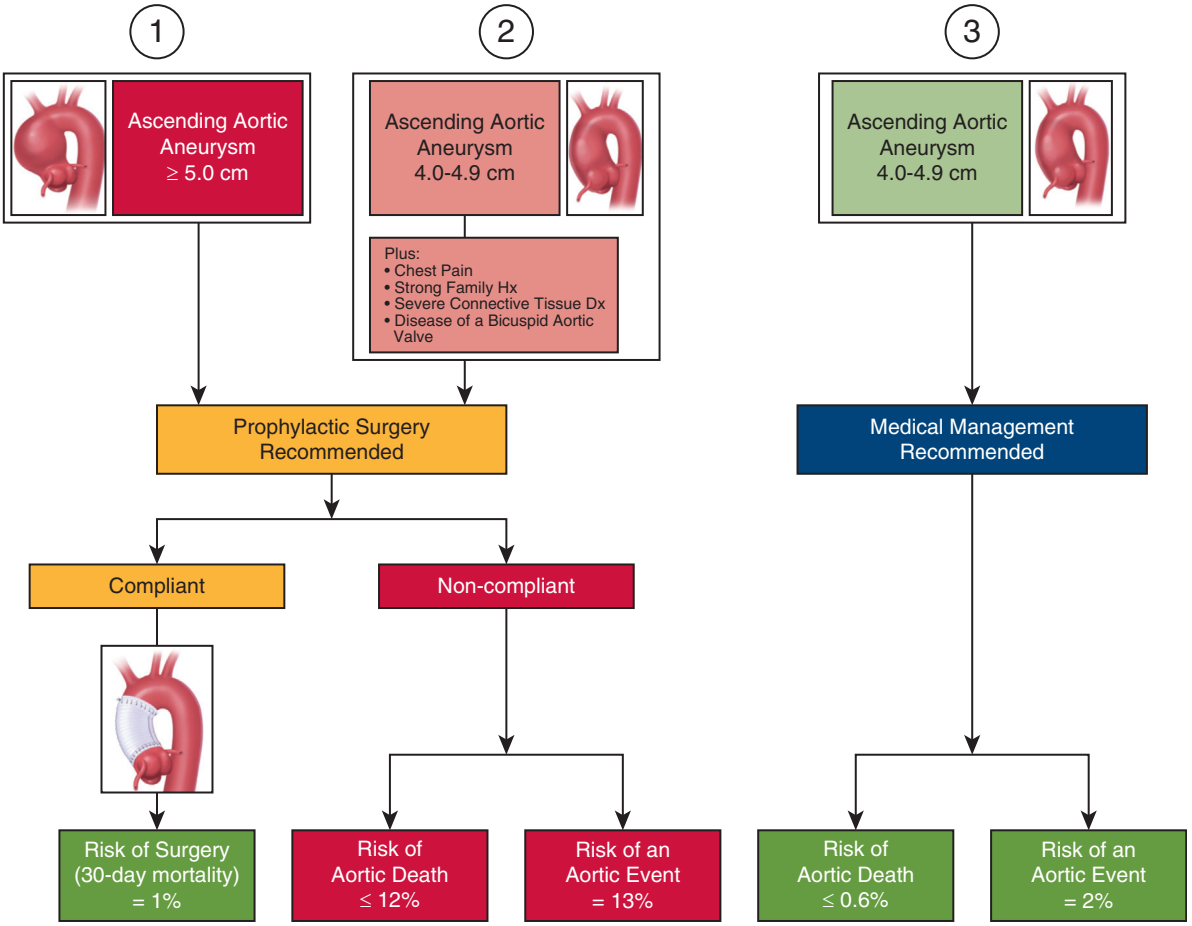


FIGURE 6. A simplified depiction of the key triage and outcomes in this study. *Dx*, Diagnosis; *Hx*, history.

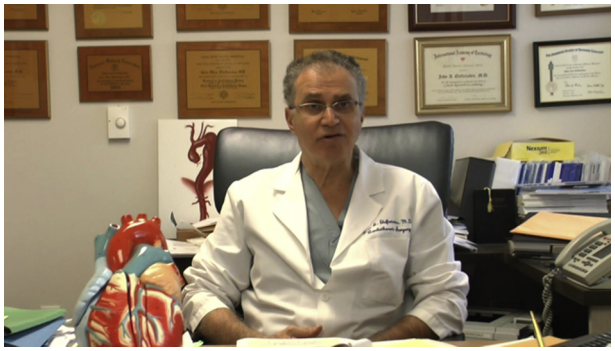
Receiver operating characteristic analysis was used to assess the sensitivity of maximal aortic diameter as a predictor of adverse aortic events within 1 year (Table 6). The model yielded an area under the curve of 0.836 for definite aortic events (95% confidence interval, 0.72-0.95; $P = .02$) and 0.983 for possible events (95% confidence interval, 0.963-1.00; $P = .001$). Likewise, high area under the curve was found while using the AHI for both definite and possible events ($P = .03$ and .005, respectively), while only significantly high for possible events when using the ASI ($P = .01$) compared with definite events ($P = .46$).

DISCUSSION

The most recent practice guidelines from the American College of Cardiology/American Heart Association recommend surgical repair of asymptomatic ascending aortic aneurysms at diameters 5.5 cm or greater (Class IC). Repair at an even smaller diameter is warranted in symptomatic patients, patients with a strong positive family history of aortic aneurysms, and patients with aggressive connective tissue diseases such as Marfan syndrome, Ehlers–Danlos syndrome, or Loeys–Dietz syndrome. In expert centers that can deliver ascending aortic surgery at low risk, surgery at 5 cm (rather than 5.5 cm) is generally accepted.[20]

In 1997, we first reported on the natural history of the thoracic aorta,[4] with the logistic regression model displaying a "hinge point" at 6 cm, at which the risk of rupture or dissection increased dramatically. Recent revisiting of these calculations, with a much larger patient cohort, proved the dominating effect of aortic size on clinical outcome. This larger analysis revealed 2 new hinge points of increased risk at 5.25 to 5.5 cm, suggesting that a "left shift" of this diameter for prophylactic surgical intervention might be necessary—to 5 cm rather than 5.5 cm (Figure 5).[8,21] This newly recommended diameter is indeed the one used in the clinical algorithm applied in the present study.

In our study, we sought to evaluate the clinical outcomes and effectiveness of a straightforward patient triaging approach for ATAA to surgery or to medical management (Figure 6). We used the aortic size criterion of 5 cm in our algorithm. This is lower than the 5.5 cm used in recent consensus documents. However,



VIDEO 1. Summary of the key points of the study and important clinical implications. Video available at: https://www.jtcvs.org/article/S0022-5223(18)32927-1/fulltext.

our most recent data support such a lower criterion. These data are presented in detail in an article in the *Journal*.[22]

The core of our algorithm is its simplicity: surgery for large or symptomatic aneurysms. The algorithm worked well in the clinical setting of new patients presenting for evaluation and management decision making. Patients triaged to medical management did well, with a low rate of aortic events. Patients triaged to surgery who could not undergo operation, for a variety of reasons, did poorly, with many aortic events and a high mortality. The triage algorithm did exactly what it needed to do—weeding out patients with high aortic risk who need surgical intervention to remain safe.

Aortic natural history studies face many obstacles. Adequate follow-up on patients can sometimes be difficult to complete. Further, because of the high fatality of aortic complications, many patients die ''suddenly'' before or just after reaching an emergency department; such patients are frequently misdiagnosed as myocardial infarctions. Therefore, ascertaining the true cause of death for many patients can become problematic. In our study, we accounted for this variable by classifying death and aortic events into ''possible'' and ''definite'' categories, as suggested by Lederle and colleagues.[12]

Our results showed distinctly worse outcomes in patients who did not follow the surgical recommendation. These outcomes in terms of mortality, development of events, or eventual surgery were significantly poorer in the surgery noncompliant and overwhelming comorbidities group, compared with patients who were triaged to medical treatment from the start. This shows that the algorithm was functioning in the clinical setting, correctly identifying the patients at risk for aortic events.

Accessory analyses by regression techniques and receiver operating characteristic confirmed prior work demonstrating an overwhelmingly strong impact of aortic size on rupture and dissection rates.

Study Limitations

This study was limited by its retrospective nature by the referral bias inherent in a single study center and in the specialized aortic referral nature of our center. Triaging of patients, although highly dependent on diameter, supplemented by symptoms, was certainly affected as well by clinical judgment and instinct, which cannot be specified or quantified. Because the ''surgery noncompliant and overwhelming comorbidities'' group included not only patients refusing surgery but also patients with comorbidities precluding safe surgery or advanced age, it is possible that this factor on its own biased against survival. With extreme critical caution in classifying an event as ''aortic,'' the number of such events may have been underestimated.

CONCLUSIONS

We have evaluated the clinical effectiveness of the specific triaging algorithm for thoracic ascending aortic aneurysms (see summary in Video 1), permitting the following conclusions:

- Patients who did not follow the surgical recommendations experienced poorer outcomes in terms of death, adverse events, and eventual surgical repair.
- Patients who were triaged to medical treatment did well, with significantly lower mortality, and had no definite aortic events.
- The clinical algorithm, based on aortic diameter and symptoms (pain), functioned extremely effectively in a clinical setting.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/18May01/28ABC%202.Aortic%20Endovascular/S86%20-%20Part%202/S86_4_webcast_045149735.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: thoracic aorta, thoracic aortic aneurysm, natural history, aortic dissection, aortic rupture, clinical outcomes, clinical care, decision making

Discussion

Dr E. Chen *(Atlanta, Ga)*. I congratulate you on this outstanding study and great presentation. This project is the latest contribution from an ongoing effort spanning over 2 decades from the Yale group to help us all better understand the natural history of thoracic aortic pathology, as well as provide recommendations for treatment algorithms. Although there is increasing consensus that diameter may be one of several factors that we must consider to influence the occurrence of adverse events, it probably remains the most objective parameter we have at the present time. I would like to ask a few questions.

Certainly we are seeing in our institution more patients referred for possible repair of aortic pathology who need intervention in the setting of reoperative surgery, and I was wondering if you could enlighten us on how this algorithm would change for someone, say, needing an ascending root and arch who has already had previous cardiac or aortic surgery instead of redo surgery.

Dr Saeyeldin *(New Haven, Conn)*. We would be a little more tolerant of the aortic diameter if the patient had a previous cardiac surgery because of the slightly increased risk, but it would not be a major factor affecting the decision. We tend to operate routinely on patients with prior cardiac surgeries, such as an aortic valve replacement or a coronary artery bypass graft, and on other high-risk patients.

Dr Chen. Your group has also previously published on the use of ASI as a decision-making tool to determine intervention versus medical observation. Could you tell us how that might have played into the treatment algorithm here.

Dr Saeyeldin. We have indeed published on the ASI and more recently on the AHI, by indexing the aortic diameter to the patient's height; however, we do not use that nomogram often, except in the extremes of body sizes, the extremely large patients or smaller patients. Having said that, in our article we performed the statistical analysis using the height index and size index. Patients in the higher-risk groups according to the nomograms were more likely

to develop aortic events. The receiver operating characteristic curves also yielded high area under the curve with these indices. Therefore, these calculations were consistent with our previous observations.

Dr Chen. In the setting of chronic dissection of the proximal aorta, whether residual dissection after a previous repair or the diagnosis of a de novo chronic dissection previously undiagnosed, how would the presence of that disease process play into your decision making?

Dr Saeyeldin. For the purpose of uniformity, we included only patients without dissection for this algorithm. However, chronic type A AD in the patients with ascending aneurysm is rare. It can lead to a lot of scarring and increase the risk of rupture, but it is usually managed in the same way with the same diameter criteria.

Unidentified Speaker. Excellent presentation, a lot of the information that you always learn from Dr Elefteriades' group. I have 1 question and an observation that there were significant adverse events in patients who had chronic kidney disease. In our practice, I have seen a few patients who presented with type I dissection; they also had adult polycystic kidney disease. Perhaps I have a hypothesis, but probably it's not proven, that there might be a correlation of an APKD gene mutation with some aortopathy, which is probably not known. Was there any subset of population in whom you observed a significant amount of younger patients with APKD disease?

Dr Saeyeldin. Of our patients, 1 patient had polycystic kidney disease. We tend to do whole exome sequencing in our patients, and the list of genes associated with aortic aneurysms continues to grow. However, we do not exactly know an exact correlation with polycystic kidney disease and aortic aneurysms at this time.

Unidentified Speaker. I think perhaps there can be a review in which people who are at higher risk, especially with this mutation or polycystic kidney disease, can be considered for follow-up if they have any large aorta, especially at the higher risk for dissection and other complications.

Dr Saeyeldin. This is a great point, and we will definitely look into that.

ORIGINAL RESEARCH REPORT

Aortic aneurysm: A life-threatening condition in a low-resource nation

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ABSTRACT

Background: Aortic aneurysm is said to be uncommon in the black population; however, with the modification in lifestyle of the dark-skinned people, and improved diagnostic facilities in Sub-Saharan African nations, a surge in its presentation is more likely. If undiagnosed, aortic aneurysm can be catastrophic. We determined the epidemiology pattern and outcome of aortic aneurysm at our institution. **Materials and Methods:** This is a retrospective analysis of patients who presented with aortic aneurysm from 2000 to 2017. A pro forma was designed to analyze the bio data, characteristics of the aneurysms, clinical manifestation, treatment, and outcome. The Crawford, Stanford, and DeBakey criteria were used to classify the aortic aneurysm. The surgical management of the aneurysm was resection and its replacement with synthetic polytetrafluoroethylene prosthesis with antibiotic prophylaxis under general anesthesia. **Results:** A total of 17 patients were recruited, with a mean age of 62.75 ± 20.92 years. A high proportion were above 65 years, i.e., 7 (41.2%), and male gender, i.e., 10 (58.8%). The most common location of aortic aneurysm using Crawford criteria was Type IV followed by Type I, with Stanford criteria being Stanford Type B (13) and with DeBakey being Type III (3). Five operated were fusiform in shape. A higher proportion of patients, i.e., 14 (82.4%), had coexisting hypertension, and a positive history of smoking, i.e., 7 (41.2%). The 30-day mortality was 64.7%, the operative mortality was 35.3%, and three patients (17.6%) were loss to follow-up. A positive history of smoking increased the risk of dead, relative risk 3.375, 95% confidence interval 0.677–5.909, $P = 0.04$. **Conclusion:** Aortic aneurysm, though uncommon, is not a rare disease among cardiovascular disorders in a low-resource environment. The most common shape and location were fusiform and Stanford Type B or DeBakey Type III, respectively. There was associated high 30-day mortality (64.7%).

Key words: Abdominal aortic aneurysm, outcome, pattern

INTRODUCTION

Aortic aneurysm is described as a constant focal dilation of the aorta with a diameter of at least 50% more than its normal diameter.[1] However, the abdominal aorta is said to have an aneurysm when the distal aorta is dilated to a diameter larger than 3 cm.[2] Aortic aneurysms are divided into thoracic aortic aneurysms (TAAs), thoraco-abdominal aortic aneurysms (TAAAs), and AAAs. TAAs may develop at any of the aortic segments which include the aortic root, ascending aorta, aortic arch, and descending thoracic aorta.[3] Ascending aortic aneurysm may involve the aortic root and annulus and terminate distally at the origin of the innominate artery while descending TAA occurs after the takeoff of the left subclavian artery. Thoraco-abdominal aneurysms involve thoracic aneurysms extending distally to the abdomen.

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AAA can be suprarenal or infrarenal. Crawford,[4] Stanford,[5] and DeBakey[6] at different time classified aortic aneurysm based on the anatomical location.[4-7] Aneurysm can also be classified based on the shape of the bulge or the lesion. Saccular aneurysms are asymmetrical and appear on the one side of the aorta. They are usually caused by injury or a severe aortic ulcer. Fusiform aneurysms are most common and appear as symmetrical bulges around the circumference of the aorta. The AAA expands at a variable rate of 2–4 mm/year until rupture. The saccular aneurysms tend to grow more rapidly than fusiform aneurysms and often rupture and result in compression symptoms.[3,7]

The reported risk factor for the development of an aortic aneurysm includes age over 65 years, male gender, smoking, hypertension, dyslipidemia, coronary artery disease, and positive family history.[3,8] It appears to have a lower incidence in black Africans when compared to Caucasians.[3,9,10] The symptoms of aortic aneurysm are usually nonspecific and varies from dull abdomen or low back aches to severe chest pain, indicating imminent rupture.[8,11,12] The diagnosis of aortic aneurysm is often made as an incidental finding on imaging studies, such as abdominal ultrasonography or computerized tomography (CT); however, it may occasionally be visible on plain radiography if the aneurysm wall is calcified.[1,8,11]

The management of aortic aneurysm depends on the diameter at presentation, rate of growth, location, and presence of symptoms or signs that may suggest impending rupture. The current modality of management includes lifestyle modification, medical treatment (doxycycline, propranolol), open surgery, and endovascular procedures. Open surgery is performed in most low-resource countries.[10,11,13,14] However, endovascular stent grafting for AAAs has become popular in both Europe and the USA.[15] Aortic aneurysm at any segment can cause distal embolization of clot or atheromatous debris that gradually obliterate and thrombosed distal visceral and lower extremity arteries.[6,8] Advancement in imaging technology has greatly assisted in the diagnosis of aortic aneurysms. Computerized axial tomography scan (CT scan) and magnetic resonance angiography provide excellent images adequate for preoperative planning either for open or endovascular procedures. Contemporary data from western population have suggested a measurably notable prevalence of aortic aneurysms; however, reports about this disease in Sub-Saharan Africa are scanty. This retrospective study determined the pathological pattern and outcome of aortic aneurysm at our center.

MATERIALS AND METHODS

This retrospective case series included 17 patients with CT diagnosis with aortic aneurysm from June 2001 till June 2017. The study was conducted in a hospital-based setting in Lagos, Nigeria. The following data were retrieved from patient's case note; patient's age and sex, location and diameter of the aneurysm, associated risk factors, treatment, and outcome. The data collected were input into the Statistical Programme for Social Sciences (SPSS) version 21.0 for windows computer program (SPSS Inc., Chicago, IL, USA), and were analyzed.

Definitions

The aneurysm resections were described as elective when a planned procedure was performed, or urgent when rapid expansion in the size of aneurysm or the sudden onset of symptoms with a tender aneurysm on palpation necessitated operation, but at which, nevertheless, the aneurysm was intact. Aneurysmal rupture defined as leakage associated with a frank retroperitoneal or intraperitoneal hemorrhage.[16] The 30-day mortality is defined as death that occurred during or following aneurysm resection at any time during the initial hospital admission and in the first 30-day period after operation.[16]

Classification on anatomical location

Crawford in 1986 described TAAA based on the anatomical extent of the aneurysm.

Type I involves a greater proportion of the descending thoracic aorta from the origin of the left subclavian to the suprarenal abdominal aorta. Type II is the most extensive, extending from the subclavian to the aortoiliac bifurcation. Type III involves the distal thoracic aorta to the diaphragm. Type IV is limited to the abdominal aorta below the diaphragm.[4] Safi's group modified the classification by adding Type V, which extends from the distal thoracic aorta including the celiac and superior mesenteric origins but does not involve the renal arteries.[5] DeBakey classification divides dissections into:

Type I involves ascending and descending aorta (= Stanford A). Type II involves ascending aorta only (= Stanford A). Type III involves descending aorta only, commencing after the origin of the left subclavian artery (= Stanford B).[6]

Operative techniques

Open repair laparotomy was adopted for all the infrarenal AAAs using transperitoneal approach under general anesthesia relaxant technique according to the patients need. The ligament of Treitz was divided and the retroperitoneal duodenum segments were mobilized and retracted. The aneurysm sac was opened with evacuation of clots, bleeding lumbar vessels were tied off, and preclotted 20-mm polytetrafluoroethylene (PTFE) graft was laid and sutured end to end with prolene 3/0 sutures on atraumatic needle. The clamps were released

thereafter; some bleeding points at the anastomotic sites were sutured and distal embolectomy with Fogarty catheter of size 3 Fr before final closure of the distal anastomosis. The aneurysmal sac was wrapped around the graft; peritoneal cavity was generously lavaged with normal saline with a drain inserted followed with wound closure. All the patients had friendly infrarenal neck for clamping. Anticoagulation with unfractionated heparin was commenced before proximal and distal clamping. The level of anticoagulation was assessed with activated clotting time. Glyceryl trinitrate (GTN) was used to reduce the blood pressure during aortic clamping. Only one patient had intra-arterial blood pressure monitoring. At the end of surgery, the patient was transferred to the intensive care unit for critical care and elective mechanical ventilation for 48 h.

Intraoperative finding

All patients had fusiform aneurysm involving the aorta with no involvement of the common iliac arteries. Three aneurysmal sac contained clots and thrombosed inferior mesenteric arteries. In one patient, there was retroperitoneal clot with no detectable area of aneurysmal leak.

RESULTS

A total of 17 patients were recruited, with a mean age of 62.75 ± 20.92 years. A high proportion of patients were above 65 years, i.e., 7 (41.2%), and males, i.e., 10 (58.8%). The mean age in male was 59.70 ± 6.64 years compared with their female counterpart 76.00 ± 4.29 years, $P = 0.4$. The median diameter of an aneurysm was 6.7 cm (25^{th}–75^{th} percentile 6.23–7.35 cm). The most common location of aortic aneurysm using Crawford criteria was Type IV followed by Type I, with Stanford criteria being Stanford Type B (13) and with DeBakey being Type III (3) [Table 1 and Figure 1].

There were 9 (52.9%) ruptured aortic aneurysm during study; 1 (5.9%) at presentation, and 8 (47.1%) while on admission awaiting surgical intervention. Aortic dissection and aortic calcification were observed in one patient each, respectively (5.9%).

The most frequent presenting complaint was pain, i.e., 8 (47.1%), either as dull abdominal aches, i.e., 7 (41.2%) or throbbing chest pain, i.e., 1 (5.9%), followed by incidental finding in 5 (29.4%) patients; other symptoms included dysphagia hoarseness of voice and hematemesis in 1 (5.9%) patient each, respectively.

A higher proportion of patients 14 (82.4%) had coexisting hypertension, and a positive history of smoking, i.e., 8 (47.1%), while only one patient (5.8%) had associated Marfan syndrome.

Five patients (29.4%) had corrective surgery; others were managed conservatively with propanolol while awaiting surgical intervention. The 30-day mortality was 64.7%, the operative mortality was 35.3%, and three patients (17.6%) were loss to follow-up.

A positive history of smoking increased the risk of dead, relative risk 3.375, 95% confidence interval 0.677–5.909, $P = 0.04$ [Table 2].

DISCUSSION

Aortic aneurysm described as a constant focal dilatation of the aorta in its courses is not an uncommon presentation at our institution, and it was accompanied by a high mortality

Table 1: The classification of aortic aneurysm using Crawford, Stanford, and DeBakey criteria

Classification of aortic aneurysm					
Crawford (*n*=17)		Stanford (*n*=17)		DeBakey (*n*=17)	
Type	Frequency	Type	Frequency	Type	Frequency
I	2	A	4	1	2
II	1	B	13	II	2
III	1			II	13
IV	12				
V	1				

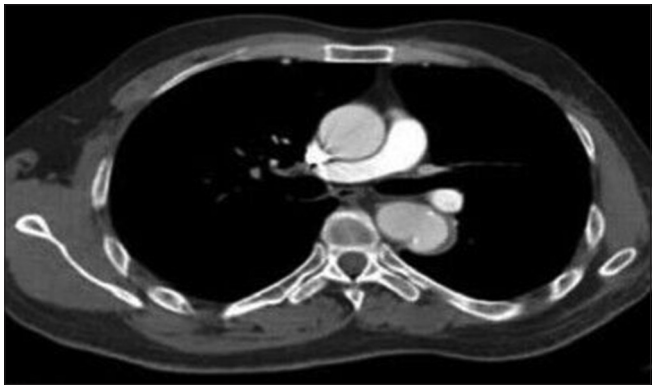

Figure 1: Abdominal aortic aneurysm

Table 2: Univariate analysis of determinants of 30 days mortality in patients with abdominal aortic aneurysm

Variables	OR	95% CI	*P* (Fisher's exact)
Age>65 years	0.29	0.04-2.32	0.25
Sex	0.88	0.11-7.11	0.66
Smoking	0.08	0.006-0.94	0.04
Alcohol	1.000	0.48-2.08	0.60
Hypertension	1.38	0.96-1.98	0.52
Rupture aneurysm	5.5	1.57-19.27	0.02*
Aneurysm size >6.5 cm	1.2	0.16-8.79	0.91
Intervention (surgery)	0.38	0.04-2.99	0.46

Values are OR, 95% CI, and *P* value (Fisher's exact). *Indicate level of significant. OR=Odd ratio, CI=Confidence interval

rate. Other scholars, however, have suggested that it is rare in the black patient[3,9] and sparse in Nigeria, with 3–5 infrarenal aortic aneurysm over a 10-year period,[10,17] It has been suggested that the low occurrence in the black Africans may not be due to a rare occurrence, but probably due to inadequate report of cases, and comatose health infrastructure in the continent.[10,13,14] However, with the changing lifestyle among black Africans, and improved diagnostic facilities, a surge in presentation is most likely.[10,14]

We observed that the mean age at presentation was around 67 years; however, three patients (17.7%) presented before the age of 40 years, and this is contrary to previous reports that the median age was between 44.5 and 56.15 years and that 21% of black Africans presented before the age of 40 years.[2,4] It has been reported that aneurysms occur 10–15 years earlier in black Africans than in Caucasians 66.3–75 years.[3,14] Bengtsson *et al*.[18] calculated the average age and sex-specific frequency of AAA based on a necropsy study of 45835 autopsies over 30 years. They observed that the frequency of AAA in men was 4.3% (two times higher than in women). In, addition, the frequency increased rapidly after the age of 55 in men, reaching a peak prevalence of 5.9% at 80–85 years, and then decreased. However, the rise in frequency started 15 years later in women than in their male counterpart, after the age of 70, reaching 4.5% in those above the age of 90 years.[18] The heterogeneity in age at presentation was attributed to varying etiology, in the elderly patient usually due to atherosclerotic changes,[1,3,13] while in the younger population, tuberculous arthritis, bacterial infection, HIV infection, trauma, and connective tissue disease were implicated.[3,9,12] This was illustrated in our study, where a 28-year-old male patient with Marfan syndrome presented with aortic aneurysm. There are, however, conflicting reports on the gender distribution,[19] while some scholars have reported a male preponderance,[9,11,17] and some suggested female preponderances;[8,19] on the contrary, a study conducted in South Africa reported that there was no gender bias.[3] The protective effect of estrogen and the negative effect of testosterone on the aorta have been proposed as a reason for the observed gender variation in those studies.[11,19] Other reasons for the heterogeneity in gender predominance included geographical location,[8,9,19] ethnicity,[9,19] and presence of comorbid conditions.[3,9]

We observed that pain (8, 47.1%) and incidental finding (29.4%) constituted a high proportion of symptom. Other included dysphagia, hoarseness in voice, hematemesis, and aortic rupture. The pain was mainly dull abdominal aches in 41.2% and throbbing chest pain in 5.9%. The presence of severe chest pain has been shown to signal imminent rupture.[8] Two patients in our study presented with complications involving the esophagus, dysphagia, and hematemesis. These are rare complications of thoracic aneurysm which is secondary to compression and erosion of the esophagus by a large aneurysm, and such occurrence is usually fatal. It is therefore not surprising that the patient with hematemesis eventually died from massive hemorrhage while that with dysphagia was lost to follow-up. A detailed history and thorough investigations would be appropriate in such atypical presentation.

We have demonstrated that aortic aneurysm was more common in the infrarenal aorta, with a high risk of occurrence in hypertensive and smokers. This is the general consensus on the characteristic of aortic aneurysm.[9,11,17] The risk factors observed with aortic aneurysm in our study included hypertension, smoking, and Marfan syndrome. This is agreement with previous studies,[3,9,10] however; other reported comorbid conditions included trauma (gunshot injury) and bacterial and HIV infections, especially in patients with femoral artery and other peripheral artery aneurysm.[3,8,13]

We observed that the diameter of an aortic aneurysm ranged from 5.5 to 8.2 cm, and this diameter was lower than a range of 8.0–15.0 cm in patients with infrarenal aortic aneurysm in an earlier study conducted in our country.[8,9] One patient in our study presented with a ruptured aneurysm; this was contrary to observation in previous studies with relatively large diameter of aneurysm.[8,9] The reason for this is unknown to the authors; however, they suggested that such huge aneurysms are sitting on a time bomb.[9] It is therefore not surprising that four patients in our cohort eventually ruptured and died while awaiting surgical intervention. Other scholars have, however, reported that the risk of aneurysmal rupture and death increases with increase in the size of the aneurysm.[20] An abdominal aorta typically enlarges at a rate of 2–8 mm/year.[20]

Five patients had surgical intervention with 40% operative mortality; this is higher than an operative mortality of 9.5% reported in Enugu.[13] The overall mortality of 64.7% is high; however, this is within the range of 26.1%–72.1% reported in other studies in the continent.[8,12,13] A positive history of smoking increased the risk of dead in our study. In our study, four patients died on the ward while awaiting surgical intervention. Variable confounding factors such as unavailability of PTFE graft, vasodilators such as GTN or sodium nitroprusside, intensive care bed space, and financial constraints were contributory. The high mortality rate observed in studies conducted in Sub-Saharan African countries; we attributed to delay in presentation and intervention due to comatose health infrastructures, and the unavailability of grafts, which are imported at presentation from Europe and America.[12,13] In countries with comatose infrastructure, continuous in-service training and upgrading of health care facilities will go a long way in reducing the morbidity and mortality associated with aortic aneurysm. To avert such preventable mortality, the United State Preventive Services Task Force recommended routine ultrasonography screening for

adults in the age range of 55–75 years.[9] The screening of men aged 65–75 years with a positive history of smoking has been reported to reduce AAA-specific mortality by 43% with an absolute risk reduction of 0.12%.[9]

Open repair laparotomy with transperitoneal approach was used in our patients with infrarenal aneurysm. This operative technique with inlay graft replacement is the most popular approach to the abdominal aorta.[21] The retroperitoneal approach, even though less widely used, was reported by many authors to be associated with reduced postoperative morbidity (such as ileus and pneumonia) and with shortened hospital stay.[21] However, endovascular aneurysm repair can be used when the facility is available and in high-risk patients.[15] This was, however, unavailable at our institution during the years in review. Five patients had surgical intervention with 40% operative mortality; this is higher than operative mortality of 9.5% reported in Enugu.[13] With the use of the Stanford classification of aortic dissection, we were only able to group 4 out of 17. Other limitation includes the retrospective nature which militates against the availability of images for and detailed data. Hence, we were unable to present some illustrations, and we could not determine confounding variables associated with the risk of developing aortic aneurysm and the outcome of aortic aneurysm.

CONCLUSION

We have demonstrated that aortic aneurysm is an emerging cardiovascular disorder in the black African, and there is need for a high index of suspicion even in a seemingly bizarre complaint.

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Conflicts of interest
There are no conflicts of interest.

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UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA – WESTERN DIVISION

MARK SNOOKAL, an individual,

Plaintiff,

vs.

CHEVRON USA, INC., a California Corporation, and DOES 1 through 10, inclusive,

Defendants.

Case No. 2:23-cv-6302-HDV-AJR

PROOF OF SERVICE

Action Filed: August 3, 2023
Trial Date: February 4, 2025

PROOF OF SERVICE

At the time of service, I was over 18 years of age and **not a party to this action**. My business address is 333 South Hope Street, 43rd Floor, Los Angeles, California 90071-1422.

On October 30, 2024, I served the following document(s): **DEFENDANT CHEVRON U.S.A. INC.'S DOCUMENT PRODUCTION, BATES NOS. CUSA000776-815.**

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I declare under penalty of perjury under the laws of the United States of America and the State of California that the foregoing is true and correct.

Executed on October 30, 2024, in Culver City, California.

H. Sarah Fan	/s/ Sarah Fan
Type or Print Name	Signature